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Stroke and coronary heart disease in relation to hyperglycemia, gender and age

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ACADEMIC DISSERTATION

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CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to the text by their Roman numerals.

I. Hyvärinen M, Qiao Q, Tuomilehto J, Laatikainen T, Heine RJ, Stehouwer CD, Alberti KG, Pyörälä K, Zethelius B, Stegmayr B; DECODE Study Group. Hyperglycemia and stroke mortality -comparison between fasting and 2-hour glucose criteria. *Diabetes Care* 2009;32:348-354.

II. Hyvärinen M, Tuomilehto J, Mähönen M, Stehouwer CDA, Pyörälä K, Zethelius B, Qiao Q; for the DECODE Study Group. Hyperglycemia and incidence of ischemic and hemorrhagic stroke-comparison between fasting and 2-hour glucose criteria. *Stroke* 2009;40:1633-1637.

III. Hyvärinen M, Tuomilehto J, Laatikainen T, Söderberg S, Eliasson M, Nilsson P, Qiao Q. The impact of diabetes on coronary heart disease differs from that on ischaemic stroke with regard to the gender. *Cardiovascular Diabetology* 2009;8:17.

IV. Hyvärinen M, Tuomilehto J, Söderberg S, Eliasson M, Stehouwer CDA, Qiao Q; for the DECODE Study Group. Age- and gender-difference in the incidence of acute CHD and ischaemic stroke in Finnish and Swedish populations. (Under review).

ABBREVIATIONS

AMI	acute myocardial infraction
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DECODE	Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe
FPG	fasting plasma glucose
HDL	high density lipoprotein
HR	hazard ratio
IDF	International Diabetes Federation
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LDL	low density lipoprotein
MAP	mean arterial pressure
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
NFG	normal fasting glucose
NGT	normal glucose tolerance
OR	odds ratio
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
TG	triglyceride
WHO	World Health Organization
2-h PG	2- hour plasma glucose

ABSTRACT

Background and aims: This study was carried out to compare the fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) criteria for diabetes with regard to their relation to stroke mortality and the incidence of ischemic and hemorrhagic stroke. In addition, the age- and gender difference in the incidence of coronary heart disease (CHD) and stroke and their relation with known cardiovascular disease risk factors and diabetes mellitus was examined.
Subjects and methods: The study was a sub-data analysis of the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study including 25 181 individuals, 11 844 (47%) men and 13 345 (53%) women aged 25 to 90 years, from 14 European cohorts.
Results: In individuals without a history of diabetes elevated 2-h post-challenge glucose was a better predictor of stroke mortality than elevated fasting glucose in men, whereas the latter was better than the former in women. Elevated FPG and 2-h PG levels were associated with an increased risk of ischemic stroke incidence. 2-h PG contributed to the risk more strongly than FPG. No relationship between hyperglycemia and the risk of hemorrhagic stroke was found. The risk of CHD and ischemic stroke incidence increased with age in both genders, but was higher in all age groups in men than in women. The gender difference was, however, more marked for CHD than for ischemic stroke. Age, smoking and diabetes contributed to the development of both CHD and ischemic stroke. Elevated cholesterol levels predicted CHD only, whereas elevated blood pressure was a risk predictor for the incidence of ischemic stroke. The CHD and ischemic stroke risk was higher in men than in women with and without diabetes, however, the gender difference diminished for CHD but enlarged for ischemic stroke in diabetic individuals. The known risk factors including diabetes contributed differently to the risk of CHD and ischemic stroke in women and in men.
Conclusion: Hyperglycemia defined by FPG or 2-h PG increases the risk of ischemic stroke in individuals without diabetes. FPG better predicts stroke mortality in women and 2-h PG in men. The risk of acute CHD and ischemic stroke is higher in men than in women in all ages, but such gender difference is more marked for CHD than for ischemic stroke. CHD risk is higher in men than in women, but the difference is reduced in diabetic population. Diabetes, however, increases stroke risk more in men than in women in all ages.

1. Introduction

Ischemic heart disease and cerebrovascular diseases are the two leading causes of disability (World Health Organization, 2003) and death in the world (World Health Organization, 2003; Lopez et al. 2006; British Heart Foundation, 2008; World Health Organization, 2008). The death rates due to the two diseases are estimated to significantly increase by the year 2030 (World Health Organization, 2008). There has been a clear decline in CVD incidence in the western industrialized countries (Kesteloot et al., 2006, Thom et al., 2006), however, in Europe cardiovascular diseases (CVDs) still account approximately half of overall mortality in both genders (British Heart Foundation, 2008). Up to 17% and 22-29% of the disability adjusted life years (DALYs) are lost due to CVDs in the western and eastern European countries, respectively (Allender et al., 2008).

CHD and stroke are commonly discussed as two diseases with similar etiology caused by atherosclerotic vascular disease (Gulcher et al., 2005). CHD and stroke have been shown to share many common risk factors such as obesity, smoking, hypertension and aging. (Wolf et al., 1991; Njolstad et al., 1996a; Njolstad et al., 1996b; Jousilahti et al., 1999; Anand et al., 2008; Jee et al., 2008). However, some differences have been reported in the risk factor profiles of the two diseases (Wilhelmsen et al., 2005). Also, some well known CHD risk factors, such as serum total cholesterol has not been found to have an association with increased risk of stroke (Bots et al., 2002; Wilhelmsen et al., 2005). Emerging evidence also indicate that the CHD and stroke risk factors may contribute differently to the development of atherosclerosis in different vascular sites in men and women (Debakey et al., 2000; Cimminiello et al., 2002; Eastwood et al., 2005; Iglseder et al., 2005; Kardys et al., 2007; Paraskevas et al., 2008; Sjölander et al., 2008).

The incidence of CVD increases with age in both genders (Jousilahti et al., 1999). However, men generally develop CVDs approximately 10 years earlier than women (Bello et al., 2004; Anand et al., 2008). Even though, the risk of developing CVD is greater in men up to middle age (Rosamond et al., 2007), the gender gap decreases with advancing age (Rosamond et al., 2008) and CVDs are a major cause of morbidity and mortality in both genders (Jousilahti et al., 1999; Seshadri et al., 2006; Bello et al., 2004; Pepine, 2004; Anand et al., 2008). Many factors either increase or decrease the risk of CVD (Kannel et al., 1961; Dobson et al., 1996). Known CVD risk factors such as hypertension, smoking, serum total cholesterol, diabetes and obesity are associated with increased risk of CHD (Jousilahti et al., 1999; Anand et al., 2008; Njolstad, 1996a) and stroke (Wolf et al., 1991; Njolstad et al., 1996b; Jee et al., 2008) both in women and in men. The known CVD risk factors are largely shared by both genders, however, some risk factors such as diabetes (Juutilainen et al., 2004), HDL-cholesterol and triglycerides (TGs) have been reported to have a greater impact on women (Shaw et al., 2006). Also, a clear gender difference has been found in the development of atherosclerosis in different arterial sites in women and men (Eastwood et al., 2005; Kardys et al., 2007).

Hyperglycemia has been found to be associated with many CVD risk factors (Glumer et al., 2003) and it has been reported to increase CVD risk both in diabetic (Håheim et al., 1995; Fuller et al., 2001) and non-diabetic individuals (Perry et al., 1994; Balkau et al., 1998; de Vegt et al., 1999; Coutinho et al., 1999; DECODE Study Group, 2003a; Levitan et al., 2004; Meisinger et al., 2006a). Even though, studies have found a clear relationship between hyperglycemia and increased risk of CHD in diabetic individuals (Orencia et al., 1997; Balkau et al. 1998; The DECODE Study Group, 2001; Danaei et al., 2006) the association

between hyperglycemia and increased risk of stroke in non-diabetic individuals is not fully elucidated (Håheim et al., 1995; Qureshi et al., 1998; Hart et al., 1999).

This thesis is a subdata analysis of the European Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe study (DECODE), including 14 cohorts from five European countries. The aim of the study was to compare the fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) criteria for diabetes with regard to their relation to stroke mortality and the incidence of ischemic and hemorrhagic stroke. In addition, the age-and gender difference in the incidence of coronary heart disease (CHD) and stroke and their relation with known cardiovascular disease (CVD) risk factors and diabetes mellitus was examined.

2. Review of the literature

2.1. Epidemiology of cardiovascular diseases

CVDs are one of the leading causes of death worldwide. The main CVDs include CHD and stroke (British Heart Foundation, 2008; World Health Organization, 2008). In 2004 ischemic heart disease and cerebrovascular diseases accounted for 12.2% and 9.7%, of deaths worldwide, respectively. It is estimated that by the year 2030 the death rates from ischemic heart disease and cerebrovascular diseases (stroke) will increase and the two diseases will remain as the two leading causes of death in the world (World Health Organization, 2008). In the developing countries morbidity due to CVDs is double compared with that of the developed countries (World Health Organization, 2003) and the age-adjusted mortality related to CHD and stroke is increasing in some developing regions (Gaziano et al., 2007). A decline in CVD incidences has been seen in many western industrialized countries (Kesteloot et al., 2006; Thom et al., 2006), however, in Europe CVDs still account for 43% of overall mortality in men and 54% in women (British Heart Foundation, 2008). Men are at greater risk of developing CVD compared with women up to middle age (Rosamond et al., 2007). However, the incidence of CVD in women increases with age and CVDs are a major cause of death in the elderly population in both genders (Jousilahti et al., 1999; Seshadri et al., 2006). Studies have indicated that the earlier development of CVD in men can be due to a combination of several different factors such as hormonal, genetic and environmental (Mendelsohn et al., 2005; Ordovas et al., 2007; Pilote et al., 2007). A number of risk factors including hypertension, smoking, serum total cholesterol, obesity and diabetes have been associated with increased CVD risk in both genders. (Wolf et al., 1991; Njolstad et al., 1996a; Njolstad et al., 1996b; Jousilahti et al., 1999; Anand et al., 2008; Jee et al., 2008). These risk factors may however, affect men and women differently (Pilote et al., 2007). Moreover, men are generally exposed to the known CVD risk factors earlier in life, which may partly explain why men develop a CVD approximately 10 years earlier than women. (Bello et al., 2004; Pepine, 2004; Anand et al., 2008).

CHD and stroke are two diseases with common background and pathology often discussed as manifestations of atherosclerotic vascular disease (Gulcher et al., 2005). Many of the common CVD risk factors are shared by the two diseases, however, some differences in risk factor profiles for CHD and stroke risk has been reported (Wilhelmsen et al, 2005). Also, the patterns of the trend of CHD and stroke incidence have been shown to vary in a population (Kitamura et al., 2002; Truelsen et al., 2003). For example, the World Health Organization Multinational MONItoring of trends and determinants in CArdiovascular disease (WHO MONICA) study has reported that while CHD rates have decreased, stroke rates have

increased in the same population, yet the opposite has been true for other populations (Truelsen et al., 2003). CHD and stroke have some common aspects, yet the reactivity of coronary and cerebral arteries with regard to the CVD risk factors, environmental and genetic, may differ. (Puddu et al., 1995; De Bakey et al., 2000; Paraskevas et al., 2008). This may in turn imply a different pathophysiology behind the two diseases.

2.1.1. Classification of coronary heart disease and stroke

2.1.1.1. Coronary heart disease

CHD is caused by insufficient blood supply to the coronary circulation causing ischemia in the heart tissue. Carotid atherosclerosis is a strong predictor of ischemic heart disease (Johnsen et al., 2997). The presence of symptoms of myocardial ischemia, biochemical markers of myocardial necrosis, and electrocardiographical findings are important in diagnosis of the disease (Alpert et al., 2008). In the latest version of International Classification of Diseases-10 (ICD-10), an international standard diagnostic classification for diseases, ischemic heart disease is classified into angina pectoris, acute myocardial infarction, subsequent myocardial infarction, complications following acute myocardial infarction, other acute ischemic heart disease and chronic ischaemic heart disease (World Health Organization, 2006).

2.1.1.2. Stroke

The clinical term stroke refers to three main categories of cerebrovascular diseases: thrombosis, embolism, and hemorrhage. Brain ischemia and infarction result from impaired blood flow and thus oxygenation to the brain whereas hemorrhage is caused by a rupture of the blood vessels in the brain (Frosch et al., 2005). Stroke registers define stroke as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than a vascular origin” (WHO MONICA Manual, 1999; Tolonen et al., 2002). The main subtypes of stroke include ischemic and hemorrhagic stroke. The two stroke subtypes have different background and pathophysiology (Collins et al., 2007). In the ICD-10 the cerebrovascular diseases include subarachnoid hemorrhage, intracerebral hemorrhage, other nontraumatic intracranial hemorrhage, cerebral infarction, stroke not specified as hemorrhage or infarction and occlusion or stenosis of precerebral or cerebral arteries, not resulting in cerebral infarction and other or sequlae of cerbrovascular disorders in diseases classified elsewhere (World Health Organization, 2006).

Ischemic stroke

Brain uses 20% of the body’s total oxygen consumption. Impaired or cessation of blood flow to the brain may result in brain ischemia due to a impaired oxygen flow to the brain tissue. This can result from the reduction of perfusion pressure in the brain or from an obstruction of one or more of the brain vessels or from both of the conditions together causing an ischemic stroke (Frosch et al., 2005). The causes for acute ischemic stroke are much more variable than for acute myocardial infarction (Fisher et al., 2008). Large-artery atherosclerosis, caused by atherosclerosis in the internal carotid or vertebral-basilar arteries (Fisher et al., 2005), small-vessel disease with formation of microatheroma in deep, small penetrating arteries and cardioembolism are the main causes of acute ischemic stroke (Fisher et al., 2008). About 70 to 88% of all strokes are ischemic (Foulkes et al., 1988; Thrift et al., 2001; Thom et al., 2006).

Hemorrhagic stroke

Intracerebral hemorrhage

Hemorrhagic stroke occurs as a result of rupture in a cerebral blood vessel, which causes bleeding into the brain tissue i.e. intracerebral hemorrhage (Collins et al., 2007). Intracerebral hemorrhage can occur at any site of the brain (Frosch et al., 2005). Hemorrhages most commonly occur in the cerebral lobes, basal ganglia, thalamus, brain stem and cerebellum (National Institute of Neurological Disorders and Stroke, 1990; Morris et al., 1999). Hypertension is a common cause for intracerebral hemorrhage (Qureshi et al., 1997; Woo et al., 2002; Ariesen et al., 2003). Intracerebral hemorrhage accounts for approximately 9 to 15% of all strokes (Foulkes et al., 1988; Thrift et al., 2001;Thom et al., 2006).

Subarachnoid hemorrhage

The most common cause of subarachnoid hemorrhage is a ruptured saccular aneurysm. Other causes include vascular malformations, (National Institute of Neurological Disorders and Stroke, 1990; Frosch et al., 2005) hematologic disturbances (Frosch et al., 2005) and tumors (National Institute of Neurological Disorders and Stroke, 1990; Frosch et al., 2005). Approximately 3 to 13% of all strokes are due to subarachnoid hemorrhage (Foulkes et al., 1988; Thrift et al., 2001; American Heart Association, 2006).

2.1.2. Coronary heart disease and stroke in the general population

The CHD mortality and incidence rates vary greatly between countries, but a clear male prominence can be observed throughout populations of different countries (Barrett-Connor et al., 1997). The CHD prevalence rises with increasing age in both genders. However, the rise is less pronounced in men compared with women aged 85 years and above (Ahto et al., 1998). The CHD incidence rates have declined significantly in many western industrialized countries (Immonen-Räihä et al., 1996; Rosamond et al., 1998; Yusuf et al., 2001). A recent Finnish cross-sectional health examination survey among Finnish adult population (aged >= 45 years) in 1980 and 2000 reported CHD prevalence to have decreased among individuals aged 45 to 64 years (Kattainen et al., 2006). Similar results were found in another Finnish study including 1 250 Finns aged 65 to 74 years. A statistical significant decline from years 1978-90 to 1997 in the prevalence of CHD was observed both in men (34.6 vs. 23.1) and in women (23.1 vs. 17.8) (Kattainen et al., 2002). The FINAMI study, a continuation of the Finnish Monitoring of Trends and Determinants in Cardiovascular Disease (FINMONICA project) examined trends in CHD mortality in women and men aged 35–64 years between years 1983 and 1997. The study found the mean annual decline in CHD mortality to be 6.4% among men and 7.0% among women (Salonen et al., 2003). However, even though the overall prevalence of CHD had decreased in individuals aged >=45 years the Finnish cross-sectional health examination survey found an almost 20% increase in the total numer of individuals with CHD. The study also reported that the dominance of CHD prevalence in middle aged men had changed to elderly women (Kattainen et al., 2006). In Finland the CHD incidence rates have also been reported to have declined less in women aged <55 years compared with men of the same age (Lehto et al., 2007), but in contrast the prevalence of CHD to have declined more clearly among elderly women (aged 64 to 71 years) than elderly men (Hartikainen et al., 2003). The FINMONICA study found the clear decline in CHD mortality rates in Finland to be due to declines in the incidence, recurrence, and case fatalities of CHD, which could be

attributed to improved primary and secondary prevention measures as well as in acute coronary care (Salomaa et al., 1996).

As with CHD, great variations exist in the stroke incidence and mortality rates across different populations and different countries (Wolfe et al., 2000; Truelsen et al., 2003). However, in most populations the stroke cases most commonly occur in individuals aged 64 years and over (World Population Prospects, 2004). Both in women and in men the number of stroke cases increase with increasing age. Stroke rates are generally higher in men compared with women (Truelsen et al., 2006) except in individuals aged 75 years and above among whom stroke rates have been reported to be higher in women (Numminen et al., 1996; Thorvaldsen et al., 1999; Correia et al., 2004). The FINMONICA study reported a clear decline in stroke incidence and mortality in between 1983 and 1992 in women (-2.2% and -4.7% per year, respectively) and men (-1.7% and -5.2% per year, respectively) in three provinces in Finland. The study included individuals aged 25 to 74 years (Tuomilehto et al., 1996a). Similar results were found in the Danish MONICA Study including residents (ca.330 000) of 11 municipalities in Copenhagen County (Thorvaldsen et al., 1999), aged 25 years or above. The age-adjusted stroke rates decreased 3.9% and 4.1% per year among men and women respectively during a 10-year period (from 1982 to 1991). However, the prevalence of stroke cases in the population remained largely the same due to an increased proportion of elderly people in the study population during the study period (Thorvaldsen et al., 1999).

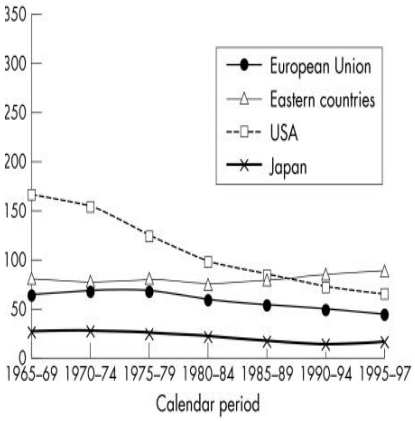
The International Stroke Incidence Collaboration Study including 11 studies from Europe, Russia, Australasia, and the United States, found no significant differences in the incidence of stroke subtypes between different geographical regions. However, the populations included in the study were nearly all western and consisted mainly of white individuals (Sudlow et al., 1997), thus a similar study including more ethnic groups may provide different results. Studies have though, reported gender differences in the incidence rates of subtypes of stroke. The ischemic stroke and intracerebral hemorrhage have been reported to be higher in men than in women, and the rates of subarcahnoid hemorrhagic stroke higher in women than in men (Truelsen et al., 2006).

CHD is the most common cause of mortality in Europe in individuals under the age of 75 years. CHD accounts for approximately 20% of all deaths from all causes in men and 19% in women before the age 75 years, accounting for over 900.000 deaths in Europe (British Heart Foundation, 2008). In Finland the risk from dying to CHD has declined since the 1970's, however, CHD still accounts for 11% and 20 % of overall deaths in women and men aged 25 to 75 years, respectively (Statistics Finland, 2007). Age standardized mortality from CHD in women and men (**Figure 1a and Figure 1b**) has declined in the European Union after the mid 1980's. The mortality trends are similar in USA and Japan. However, in most of the Eastern Europe CHD mortality has been rising in both genders (Levi et al., 2002).

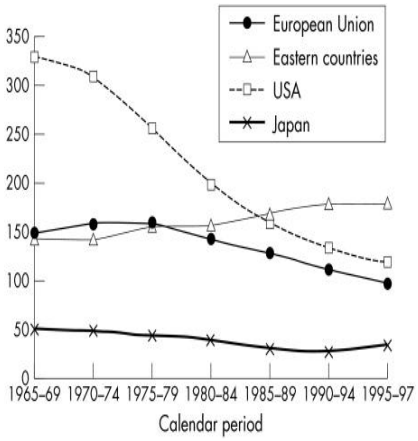
In Europe stroke accounts approximately 500,000 deaths in individuals under the age of 75 years. Of death from all causes in men 9% and in women 8% are due to stroke in people under the age 75 years (British Heart Foundation, 2008). The age standardized mortality from cerebrovascular diseases has declined in the European Union in women (**Figure 1c**) and in men (**Figure 1d**). The trends are similar in USA and Japan. However, in most Eastern European countries mortality from CVDs including cerebrovascular diseases has been increasing in both genders (Levi et al., 2002).

Coronary heart disease

a Women

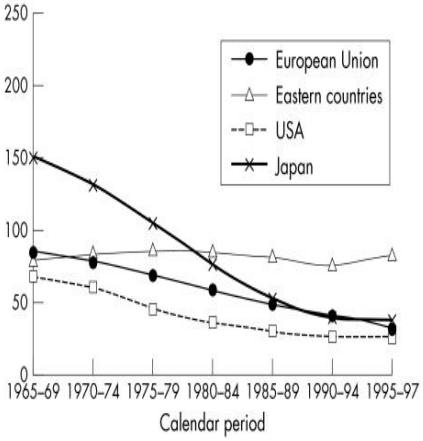


b Men



Stroke

c Women



d Men

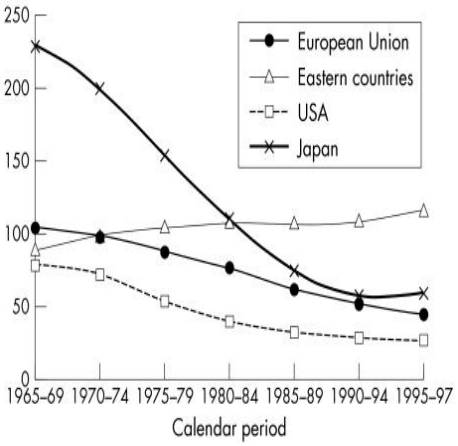


Figure 1. Age standardized (world population) mortality rates during the years 1965 to 1997 from CHD and stroke in women (**Figure 1a and Figure 1c**) and men (**Figure 1b and Figure 1d**) in the European Union, eastern European countries (Bulgaria, Czech Republic, Hungary, Poland, Romania, and Slovakia), the USA, and Japan (Modified from Levi et al., 2002).

2.1.3. Secular trend in the incidence and mortality from coronary heart disease and stroke

The WHO MONICA project measured CHD mortality trends in 37 populations around the world, including 29 European populations from the early 1980s over ten years (Tunstall-Pedoe et al., 1999). The study included men and women aged 35-64 years. The most significant decrease in coronary-event rates in men occurred in three northern European populations with the greatest decline in North Karelia, Finland. The increase in coronary event rates both in male and female populations occurred mainly in Central and Eastern Europe and Asia (Tunstall-Pedoe et al., 1999). The FINMONICA study described a 55% decline in the incidence of myocardial infarction in men and 62% in women, and 66% and 81% decline in CHD mortality, respectively between years 1972 to 1992 (Immonen-Räihä et al., 1996). A more recent Finnish study (Pajunen et al., 2004) examined the trends in CHD incidence and mortality in Finland during a 11-year period (from 1991 to 2001). The study found the average decline in fatal and nonfatal CHD events per year to be 5.2% among men and 6.1% among women (Pajunen et al., 2004). A clear decreasing trend in the CHD incidence and mortality has been observed in the western industrialized world over the past 30 years (Immonen-Räihä et al., 1996; Rosamond et al., 1998; Yusuf et al., 2001). However, in many Eastern European countries such as Ukraine, the Russian Federation and Hungary the trend has been increasing and they have one of the highest rates of CVD incidence and mortality in the world (Yusuf et al., 2001).

A deep decline in stroke mortality has occured in many western industrialized countries (Gale et al., 1997; Sarti et al., 2000; Lawlor et al., 2002). However, recently in some countries the rate of the decline has been reported to slow down (Gillum et al., 1997; Sarti et al., 2000; Feigin et al., 2003). In most industrialized countries stroke mortality started to decline in the beginning of the 1950s and the decline clearly increased in the early 1970s. From 1970s to mid 1980s stroke mortality rates have fallen by 30 % in most western countries and over 50% in for example USA and Japan. However, in many Eastern European countries stroke mortality has remained stable or even increased. For example, in Poland and Hungary stroke mortality among men increased over 50% from 1970 to 1985 (Gale et al., 1997). A recent international epidemiological study (Sarti et al., 2000) based on WHO mortality data, examined secular trends in stroke mortality from 1968 to 1994 in individuals aged 35 to 84 years. The study found great differences in stroke morbidity and mortality trends in different regions of the world. In most western countries a decline in stroke mortality was observed in the early 1970s, with further increase in the decline in the 1980s. The decline in stroke morbidity and mortality continued to the early 1990s. In some countries, for example Sweden and Danemark, the decline in stroke mortality trend slowed down by the end of the study period, especially in the last five years from 1989 to mid 1994. In countries that still had moderate to high stroke mortality rates between 1990 and 1994, for example Finland and Japan, a declining mortality trend was still observed. In some Eastern European countries, for example Poland and Bulgaria the stroke mortality trends among men were increasing during the whole study period. The direction of the stroke mortality trends were the same for both young people and the elderly population (in men $r=0.85$, $p=0.0001$ and in women $r=0.85$, $p=0.0001$), even though the relative change was smaller among the older people (Sarti et al., 2000).

2.1.3.1. Gender, secular trend, coronary heart disease and stroke

Gender difference related to CHD incidence and mortality is well known (Lerner et al., 1986; Jousilahti et al., 1999; Anand et al., 2008). A recent epidemiological study including six countries (England and Wales, Australia, France, Japan, Sweden and the United States) examined secular trends in gender differences from CHD mortality in between 1947 to 1997. The study found the gender difference in CHD mortality to vary over time and geographically. The high prevalence of CHD in the 20th century affected mainly men which to a large extent resulted from differences in risk factor profiles in men and women such as smoking, hypertension, alcohol use and fat consumption (Lawlor et al., 2001). The study concluded that the widely proposed protective effect of endogenous estrogen in women does not explain the gender difference in CHD development, but environmental factors are important (Lawlor et al., 2001).

A gender difference in stroke risk has been reported in general population (Sarti et al., 2000; Truelsen et al., 2006). In countries where the stroke mortality trends (in individuals aged 35 to 74 years), such as Poland and Bulgaria, have been increasing the trend has been found to be more favorable for women than for men. Similarly, in countries where the mortality trend has been declining the decline has been greater in women than in men. Still, the direction of the trend has been found to be the same in women and in men in individuals aged 35 to 74 years ($r=0.95$, $p= 0.0001$) and in individuals with advanced age 75 to 84 years ($r=0.92$, $p=0.0001$) (Sarti et al., 2000).

2.2. Cardiovascular disease risk factors

It is well established that certain factors either increase or decrease the risk of CVD (Kannel et al., 1961; Dobson et al., 1996). Many risk factors such as hypertension, smoking, serum total cholesterol, diabetes and obesity have been associated with increased risk of CHD (Jousilahti et al., 1999; Anand et al., 2008; Njolstad, 1996a) and stroke (Wolf et al., 1991; Njolstad et al., 1996b; Jee et al., 2008) in both genders. Even though, many of the well-known CVD risk factors are shared by both genders, studies have indicated that many CVD risk factors such as diabetes (Juutilainen et al., 2004), high-density lipoprotein cholesterol (HDL-cholesterol) and TGs have greater impact on women (Shaw et al., 2006). Emerging evidence show that the known CVD risk factors may affect different arterial sites differently (Debakey et al., 2000; Cimminiello et al., 2002; Paraskevas et al., 2008). A Swedish population based study with 28 years of follow-up, comprising of 7 400 Swedish men aged 47-55 years, found several differences regarding incidence, mortality, prognosis, and risk factors between CHD and stroke (Wilhelmsen et al., 2005). Also, the WHO MONICA study found CHD rates to decrease while stroke rates increased in one population while in another population the opposite was observed (Truelsen et al., 2003). The findings would indicate different pathologies and thus different risk factor profiles behind the two diseases. Yet, another study, including 18 662 US male physicians aged 40-84 years, compared competing risk factors for CHD, stroke and venous thromboembolism. The study found that the known risk factors; hypertension, elevated cholesterol, diabetes, and smoking were comparable for CHD and stroke, but not for venous thromboembolism. However, the risk factors in the study were self-reported, which could cause some bias in the measurements and also bias in analyzing the results (Glynn et al., 2005).

Recent evidence indicate that the known CVD risk factors contribute differently to the development of atherosclerosis and thus CVDs in women and men. (Eastwood et al., 2005; Iglseder et al., 2005; Kardys et al., 2007; Sjölander et al., 2008). In a population based study in Rotterdam, including 2 013 women and men, aged 55 years and above, gender differences in CVD by vascular site were compared by comparing degrees of atherosclerosis in different arteries. The study found that the gender difference in atherosclerosis was larger in coronary vessels than in other vascular sites. This gender difference was more pronounced in younger individuals, but remained present even in individuals of advanced age (Kardys et al., 2007). Furthermore, the Salzburg Atherosclerosis Prevention program, (a prospective study to evaluate the effect of genetic and metabolic factors in the development of atherosclerosis) including 1 001 men (aged 40 to 55 years) and 587 women (aged 50 to 65 years) found the metabolic syndrome, defined according to NCEP-ATPIII criteria (NCEP, 2001), to affect early atherosclerosis more profoundly in women than in men. The odds ratio (OR) for women was 2.05 [confidence interval (CI) 95% 1.17 to 3.59] and for men 1.11 (CI 95% 0.72 to 1.73). The analyses were adjusted for age, body mass index (BMI), low-density lipoprotein cholesterol (LDL-cholesterol) and smoking (Iglseder et al., 2005).

2.2.1. Secular changes in risk factors for coronary heart disease and stroke

The CVD risk factor trends vary by population and gender (Evans et al., 2001). The WHO MONICA project including 21 countries in four continents found variations in trends in the known CVD risk factors among populations both in women and in men. For example, cigarette smoking decreased in most populations in men, and increased in most populations in women especially in the eastern European countries. The total cholesterol levels decreased in approximately 50% of the male populations and majority of the female populations, but the 10-year trend in BMI increased in half of the female and male populations (Evans et al., 2001). The changes in the classic risk factors have been proposed to explain part of the change in trends in CVD morbidity and mortality in populations. Another WHO MONICA study including 38 populations from 21 countries examined the changes in trends in risk factors between mid-1980s to mid-1990s and to what extent these changes explain the changes in CHD incidence in women and men aged 35 to 65 years. The study found the overall variety in risk factor trends to be similar to CHD event rates. However, the study concluded that the change in coronary-event rates that could be explained by trends in the known CVD risk factors were low, approximately 15% for women and 40% for men (Kuulasmaa et al., 2000). A recent Finnish study found the CHD mortality rates to have declined approximately by 63% between years 1982 to 1997. The study found that approximately 23% of the decrease in mortality was attributed to improvements in treatment. The improvements in risk factor profiles explained approximately 52-72% of the reduction in CHD deaths during the study period (Laatikainen et al., 2005). Similarly, the WHO MONICA study examining the trends in stroke incidence in 15 populations from nine countries in individuals aged 35 to 64 years, found the changes in trends in classic risk factors only partly to explain the variations in stroke trends in different populations. During the 10-year study period, taking the time lag into account, approximately 9% of the variation of stroke rates in men and 36% in women could be explained by changes in risk factor trends. The study found the association between changes in classic risk factors and stroke trends to be more marked in women than in men (Tolonen et al., 2002).

In the WHO MONICA study approximately two-thirds of the decline in CHD mortality was found to be due to decrease in incidence rates (possibly related to decrease in the risk factor levels) and one third in case fatality (possibly related to improved coronary care) rates

(Tunstall-Pedoe et al., 1999). Similar results were found in a study conducted in United Kingdom between early 1980s and 2000. Approximately 42% of the decrease in CHD mortality rates was attributable to better treatments and 58% to reductions in the known risk factors, mainly smoking, blood pressure and cholesterol levels (Unal et al., 2004). Men generally develop CHD approximately 10-years earlier than women (Lerner et al., 1986; Anand et al., 2008). Several factors may play a role in the differences in CHD mortality and morbidity in women and men. A population based study including 14 786 Finnish men and women found gender differences in the known CVD risk factors to explain almost 50% of the gender related differences in CHD incidence and mortality. The study found the greatest difference in the risk factors between genders to be the HDL/total cholesterol ratio, but also a greater prevalence of smoking among men contributed to the the excess CHD risk in men compared with women (Jousilahti et al., 1999). Other factors such as genetic predisposition together with environmental factors may affect the development of CVD in both genders (Ordovas et al., 2007; Pilote et al., 2007). The gender gap in CHD incidence and mortality diminishes with advancing age (Jousilahti et al., 1999; Rosamond et al, 2007; Andreotti et al., 2008) and in the elderly population, at least partly due to the longer life span in women the number of CHD events is higher in women compared with age-matched men. Gender differences in CHD mortality can also be explained by the different treatment strategies for men and women with CHD. Women with CHD are often underdiagnosed and undertreated compared with men (Andreotti et al., 2008).

The mortality rates for stroke and stroke subtypes differs with regard to gender (Sacco et al., 1998; Ayala et al., 2001) and age (Ayala et al., 2001). Age- specific incidence and mortality rates are higher in men than in women. However, due to the longer lifespan in women stroke events are higher in elderly women compared with age-matched men (Sacco et al., 1997). In an epidemiological study among United States residents between years 1995 to 1998 mortality rates (per 100 000 population) were calculated to compare gender- and age-standardized death rates for ischemic stroke, intracerebral and subarachnoid hemorrhagic stroke. The study found the female-to-male ratio for stroke mortality to be 0.9 for ischemic stroke, 0.8 for intracerebral hemorrhage and 1.6 for subarachnoid hemorrhage. The age-specific mortality rates were lower for women than for men under the age of 65 years, however the mortality rates for ischemic stroke were higher in women in individuals over 65 years. The risk of mortality from subarcahnoid hemorrhage was higher in women than in men across age groups and the gender difference increased with increasing age (Ayala et al., 2002). Another study anlyzed the distribution of stroke subtypes in 1 581 individuals with first ever acute stroke in Barcelona between years 1995 to 2002. The study found no differences between ischemic (85.8% in women vs. 83.7% in men) and hemorrhagic stroke (14.2% vs.16.3% in men) with regard to gender. However, significant gender-differences were found in the incidence of subtypes of acute ischemic stroke classified according to TOAST (Trial of Org 10172) (TOAST, 1998). Women had more cardioembolic strokes and men more atherothrombotic and lacunar strokes. The study concluded that the greater frequency of known atherosclerotic risk factors, such as smoking and arterial peripheral disease could explain the predominance of atherothrombotic strokes found in men in the study. Additionally, the higher percentage of cardioembolic strokes among women compared with men could be due to greater frequency of atrial fibrillation found in women. Other gender differences in risk factors in individuals suffering first ever acute stroke were the predominance of arterial hypertension in women, and excess alcohol use, smoking, and history of arterial peripheral disease in men. The study found no differences regarding diabetes, history of ischemic heart disease or hypercholesterolemia in between genders (Roquer et al., 2003).

2.2.2. Age

CVD incidence and mortality has been found to increase with aging in both genders (Kannel et al., 1961; Jousilahti et al., 1999). Aging is one of the most significant risk factors for CHD (Jousilahti et al., 1999) and stroke (Wolf et al., 1992; Brown et al., 1996). Approximately 82% of individuals who die of CHD are aged 65 years or above. Even though, the mortality risk from CHD in women lags 10 years behind men, the gender gap decreases with advancing age (Rosamond et al., 2008). Stroke rates more than double for every 10 years after the age 55 in women and men (Wolf et al., 1992; Brown et al., 1996). The Framingham Study found the lifetime risk of stroke to be 1 in 6 or higher in individuals aged 55 to 75 years. The risk was higher in women (20% to 21%) than in men (14% to 17%), mainly due to the longer life expectancy in women. Elevated blood pressure significantly increased the lifetime risk of stroke (Seshardi et al., 2006). The Framingham study has found a fall in diastolic blood pressure and a rise in systolic blood in individuals above the age of 60 years. This is consistent with increased large artery stiffness due to aging and thus increased risk of CVD (Franklin et al., 1997). Furthermore, metabolic changes such as increased risk of insulin resistance, diabetes, changes in lipid metabolism and increase in BMI occur with aging, which all in turn are associated with increased CVD risk. (Barbieri et al., 2001; Wilson et al., 2002b; Zeeh et al., 2002; Schubert et al., 2006).

2.2.3. Gender

CHD rates vary greatly between different populations, however, the age-standardized male-to-female ratio of 2.5 to 4.5 remains fairly consistent across populations (Barrett-Connor et al., 1997). The reasons for this gender gap are not fully known (Sytkowski, 1996; Jousilahti et al., 1999; Anand et al., 2008). The Framingham study examined 20-year trends in risk factors, incidence, and mortality among women and men aged 50-59 years. The study found that improvements in the known risk factors (cholesterol, blood pressure, diabetes, smoking and obesity) could explain approximately half of the 51% decrease in CHD mortality in women and one third to one half of the 44% decrease in men observed during the study period. However, these risk factors could not explain the observed gender difference in CHD incidence (Sytkowski, 1996). In another study consisting of 14 786 Finnish men and women, aged 25 to 64 years, the differences in risk factors between women and men, such as HDL cholesterol and smoking, explained almost 50% of the gender difference in CHD risk. The observed age related increase in CHD incidence and mortality in the study could be attributed to an increase in risk factor levels (serum total cholesterol levels, blood pressure, BMI, and diabetes prevalence) with advancing age in both genders. However, the risk factor related increase in CHD with age was more pronounced in women than in men (Jousilahti et al., 1999). The INTERHEART study, a global case-control study, consisting of 27 098 participants from 52 countries, examined the differences in risk factor profiles in women and men in different age groups to find out why women develop acute myocardial infarction approximately ten years later then men. The study found that in women the risk factors hypertension, diabetes, physical inactivity, and alcohol use more strongly predicted the development of acute myocardial infarction than in men. In the study the risk of acute myocardial infarction was significantly higher in men compared with women before the age of 60 years. However, when the analysis was adjusted for the risk factor levels present in women and men the gender difference was reduced by over 80%. The study concluded that the 10 year lag in acute myocardial infarction in women can be explained by higher levels of risk factors at a younger age in men compared with women (Anand et al., 2008). Furthermore, the protective effect of estrogen has been proposed to be correlated with decreased risk of

CVD mortality and morbidity in premenopausal women compared with age-matched men (Klouche et al., 2006).

The gender difference in the lifetime probability for CHD is greater than for total CVD in general population (Peeters et al., 2002). The risk of stroke is only slightly increased in men compared with women and the stroke incidence rates are approximately 1.25 times higher in men. Due to the longer lifespan in women the annual mortality rates are higher in women. (Sacco et al., 1997a; Peeters et al., 2002).

2.2.4. Hyperglycemia and type 2 diabetes mellitus

Diabetes mellitus is a disorder which is characterized by persistent elevated blood glucose levels in the body due to lack of insulin or insulin resistance in the periphery (World Health Organization, 1999). Diabetes has clearly been shown to increase the risk for CVD event in all age groups and both in women and in men (Kuller et al., 2000; Abbott et al., 2003; Juutilainen et al., 2004; Kissela et al., 2005; Barr et al., 2007). The prevalence of type 2 diabetes is increasing among adults worldwide (Wild et al., 2004; Lusignan et al., 2005).

Hyperglycemia refers to abnormalities in glucose metabolism that are most commonly measured with threshold criteria for fasting plasma glucose (FPG) or 2-h plasma glucose (2-h PG, measured two hours after a 75 gram oral glucose load). Patients with hyperglycemia are at increased risk of developing type 2 diabetes (Petersen et al., 2005) and CVD (Haffner, 1998; Coutinho et al., 1999; de Vegt et al., 1999; DECODE Study Group, 2003 a). Hyperglycemia and diabetes are discussed in more detail below.

2.2.5. Overweight and obesity

Overweight and obesity are increasing in western societies (Berg et al., 2005; Bornstein et al., 2008). Total body fat and visceral adiposity increase with age. The age related increase in adiposity is higher in women than in men (Poehlman, 1995). Obesity is associated with many CVD risk factors, such as hypertension (Reeder et al., 1992; Wilson et al., 2002a), dyslipidemia (Reeder et al., 1992) and diabetes (Reeder et al., 1992; Wilson et al., 2002b; Field et al., 2004; Meisinger et al., 2006b). Overweight and obesity are associated with increased risk of CVD (He et al., 2001; Wilson et al., 2002a). The Framingham study, with 44 years of follow-up, examined association between BMI (defined as weight in kilograms divided by height in meter squared), cardiovascular disease risk factors and CVD end points in men and women aged 35 to 75 years. The primary outcome was first incident CVD event, including angina pectoris, myocardial infarction, CHD, and stroke. The study compared individuals with overweight (BMI= 25.0-29.9) and obesity (BMI >=30) with individuals with normal weight (BMI= 18.5-24.9). Excess adiposity was found to be significantly associated with CVD events both in men [overweight; relative risk (RR) 1.21 (95%CI 1.05-1.40) and obesity; RR 1.46 (95%CI 1.20-1.77)] and in women [overweight; RR 1.20 (95%CI 1.03-1.41) and obesity RR 1.64 (95%CI 1.37-1.98)] (Wilson et al., 2002a). Similar findings were obtained in the NHANES I Epidemiologic Follow-up Study, a prospective cohort study of NHANES I with 19 years of follow-up. The study included 13 643 men and women aged 25 to 74 years without a history of congestive heart failure at baseline. The study found a significant association between overweight (BMI >= 27.3 for women and BMI >= 27.8 for men) and increased risk of congestive heart failure both in women [RR 1.43 (95% CI 1.19-1.72)] and in men [RR 1.24 (95%CI 1.01-1.51)]. The analysis was adjusted for age, race, and time-dependent history of CHD (He et al., 2001).

The relationship between adiposity and cerebrovascular disease is to some extent not fully elucidated (Jood et al, 2004; Song et al., 2004; Hu et al., 2007a). In a population based study consisting of 49 996 participants aged 25 to 75 years, from Finland elevated BMI was found to be a risk factor for total and ischemic stroke. The multivariate adjusted (age, study year, smoking, physical activity, educational level, family history of stroke, alcohol drinking) hazard ratio (HR) for each 1-U increase in BMI were 1.04 (95%CI 1.02-1.05) in women and 1.05 (95%CI 1.04-1.07) in men. Abdominal adiposity defined as waist to hip ratio, was a risk factor for total and ischemic stroke in men, but not in women. In women, a U-shaped association was found between hemorrhagic stroke risk and BMI (Hu et al., 2007a). Similar findings were obtained in the prospective Multifactor Primary Prevention Study in Sweden with 7 402 male participants aged 47 to 55 years with over a 28-year follow-up. The study found elevated BMI to be associated with increased risk of ischemic stroke in men with BMI >30.0, HR 1.78 (95% CI, 1.22-2.60). However, no association was found between BMI and hemorrhagic stroke risk. Analysis were adjusted for smoking, exercise, psychological stress, occupational class, and parental history of stroke (Jood et al. 2004). Also, in women obesity has been found to be associated with ischemic stroke risk. In the Nurses Health Study including 116 759 women aged 30 to 55 years elevated BMI was associated with increased risk of ischemic stroke RR varying between 1.75 (95% CI, 1.17-2.59), 1.90 (95% CI, 1.28-2.82), and 2.37 (95% CI, 1.60-3.50) for BMI of 27 to 28.9, 29 to 31.9 kg/m^2, and 2.37 (95% CI, 1.60-3.50), respectively. Weight gain from the age of 18 was associated with increased risk of ischemic stroke. No significant association was found between BMI and the risk of hemorrhagic stroke (Rexrode et al., 1997).

In obese children CVD risk factors such as LDL-cholesterol, decreased levels of HDL-cholesterol, increased insulin levels and higher blood pressure, are more common compared with children with normal weight (Reinehr et al., 2006). Some but, not all studies (Lawlor et al., 2005a; Lawlor et al., 2006) have shown childhood obesity to be associated with increased risk of CVD in adult life (Gunnell et al., 1998).

2.2.6. Smoking

Increased mortality and disability in industrialized countries is related to smoking (Doll et al., 1994; Mokdad et al., 2004). It is estimated that globally, in the year 2000, 4.83 million people died prematurely because of smoking (Ezzati et al., 2003). Smoking rates vary greatly between different countries and different populations. The prevalence of smoking is highest in the South-East Asia and Western Pacific regions and lowest in the African and American regions (World Health Organization, 2007). The WHO MONICA study including 37 populations from 21 countries (individuals aged 35-64 years) reported the prevalence of smoking has been decreasing in majority of male populations while it was increasing in most of the female populations (Evans et al., 2001).

Studies have indicated that the progression of atherosclerosis in the carotid arteries is directly related to total pack-years of tobacco exposure, which may be cumulative and irreversible. The Atherosclerosis Risk in Communities study, a population-based study with 10 914 middle-aged adults from 4 communities in the United States enrolled between 1987 and 1989, found current cigarette smoking to be associated with 50%, past smoking with 25% increase and exposure to environmental tobacco smoke with 20% increase in the progression of carotid atherosclerosis when compared with nonsmokers. The analysis were adjusted for for demographic characteristics, known CVD risk factors, and lifestyle variables such as physical

activity and alcohol use. The stduy found the association between smoking and atherosclerosis to be more marked in individuals with diabetes and hypertension (Howard et al., 1998a). The NHANES I Epidemiological Follow-up Study found daily cigarette smoking to be associated with increased risk of congestive heart failure. The risk was 88% increased in women and 45% in men (He et al., 2001). In a meta-analysis consisting of 32 studies, smoking was associated with a significantly increased risk of stroke. There were clear difference in stroke risk according to subtype. The risk for ischemic stroke was 1.9, for hemorrhagic stroke 0.7 and for subarachnoid hemorrhage 2.9 (Shinton et al., 1989). Furthermore, smoking has been found to have a graded association with risk of type 2 diabetes independent of other risk factors, age, BMI, physical activity, blood pressure, education and drinking coffee (Patja et al., 2005).

Smoking cessation decreases CVD risk and CVD risk is reduced already one year after smoking cessation (Negri et al., 1994). The risk decreases to the levels of non-smokers within 10 years (Negri et al., 1994; Al-Delaimy et al., 2001). Even though the benefits of smoking cessation are greatest when young, (<=35 years), smoking cessation even at middle age decreases smoking related mortality substantially (Doll et al., 1994). In addition to smoking cessation, the increased morbidity and mortality that characterize smokers may be further reduced by improvements in lifestyle behaviors such as diet and physical activity. (Hashizume et al., 2000; Bernaards et al., 2003; Haveman-Nies et al., 2003).

2.2.7. Hypertension

The incidence and prevalence of high blood pressure is increasing in general public (Lorenzo et al., 2002; Hajjar et al., 2003). The prevalence of hypertension increases with age (Franklin et al., 1997; Lorenzo et al., 2002; Vasan et al., 2002) and the residual lifetime risk of developing hypertension is 90% in individuals aged 55- to 65-years (Vasan et al., 2002). Hypertension is clearly related to CVD incidence (He et al., 2001) and mortality in long-term (Stamler et al., 1989; Antikainen et al., 1998; Hart et al., 1999; Miura et al., 2001; Lewington et al., 2002; Harmsen et al., 2006). A study including the World Bank regions (Europé, central Asia, Latin America and the Caribbean, Middle East and north Africa, south Asia, and sub-Saharan Africa, low-and middle-income regions of east Asia and Pacific, and high-income regions worldwide) examined the blood pressure related burden of disease worldwide. The study found the burden to be large in all economies, but the proportion of burden attributable to high blood pressure to vary between different regions ranging from 4% to 35% for mortality and 2% to 20% for DALYs. The largest blood-pressure-related burden, for both mortality and DALYs, was found in Europe and central Asia, while it was smallest in sub-Saharan Africa (Lawes et al., 2008).

In older adults, prehypertension, defined as systolic blood pressure (SBP) from 120 to 139 and diastolic blood pressure (DBP) from 80 to 89 mmHg, frequently progresses to hypertension during a period of four years (Vasan et al., 2001a). Prehypertension is less common in women than in men (prevalence 23% vs. 40%) (Wang et al, 2004). Prehypertension is associated with increased risk of CVD. The Framingham study found 1.5 times (95% CI, 0.9 to 2.5) and 1.3 times (95% CI, 1.0 to 1.9) increased risk of CVD with SBP levels of 120 to 129 mmHg and DBP of 80 to 84 mmHg and 2.5 times (95% CI, 1.6 to 4.1) and 1.6 times (95% CI, 1.1 to 2.2) with SBP levels of 130 to 139 mmHg or DBP of 85 to 89 mmHg in women and men, respectively (Vasan et al., 2001b). Hypertension is a significant risk factor for CHD risk in both genders (Jousilahti et al., 1999; Lawes et al., 2003). A clear association has also been shown between hypertension and ischemic (Lawes et al., 2003) and

hemorrhagic (Qureshi et al., 1997; Woo et al., 2002; Ariesen et al., 2003) stroke risk. An approximately 80% increased stroke risk has been reported for every 10 mmHg increase in DBP (Prospective studies collaboration, 1995). However, with active hypertension treatment CVD incidence and mortality can be reduced in both genders (MRC, 1985; Staessen et al., 1997; Preston et al., 2007). Even small long-term reductions in blood pressure such as 5-6 mmHg DBP can reduce stroke risk over 35% (Collins et al., 1990), for individuals aged 60 to 69 years and a 10 mm Hg reduction in SBP decreases CHD risk about 24% (Lawes et al., 2003).

Type 2 diabetes and elevated blood pressure often coexists (Gress et al., 2000; Isomaa et al., 2001; Ball et al., 2003; Schrier et al., 2007). Studies have shown a strong relationship between elevated blood pressure and a risk of micro-and macrovascular complications in type 2 diabetes (Adler et al., 2000). Elevated blood pressure is a major risk factor for ischemic heart disease (Turner et al., 1998; Fuller et al., 2001) and stroke also in diabetic individuals (Fuller et al., 2001).

2.2.8. Dyslipidemia

Abnormal lipid levels are clearly correlated in the development of atherosclerosis (Levine et al., 1995; Kowalska et al., 2001). Several studies have shown a significant association between abnormal serum lipid levels and increased risk of CVD (Gardner et al., 1996; Isles et al., 2000; Anand et al., 2008). CHD risk is significantly increased in individuals with elevated plasma cholesterol, TG and LDL-cholesterol levels as well as low HDL-cholesterol levels. (Lamarche et al., 1995; Lamarche et al., 1996). Also, increased lipoprotein (a) levels have been found to be an independent risk factor for the development of coronary artery disease (Wild et al., 1997) especially in individuals with other known CVD risk factors such as obesity, type 2 diabetes, arterial hypertension and smoking (Zlatohlavek et al., 2008). Lipid abnormalities have also been shown to precede the onset of hypertension in nondiabetic individuals (Haffner et al., 1996; Halperin et al., 2006) and thus increase the risk of CVD. In a recent meta-analysis including 90 056 individuals from 14 studies, one mmol/l decrease in LDL-cholesterol levels using statin therapy was found to decrease the 5-year incidence of major coronary events and stroke by 20% (Baigent et al., 2005).

Whether elevated serum cholesterol levels increase the risk of stroke is not fully elucidated (Papadakis et al., 1998; Wannamethee, 2000; Wilhelmsen et al., 2005). The Womens Health study including 27 937 women, examined the association between lipids levels and the risk of ischemic stroke in healthy middle-aged women aged ≥45 years. The study found a significant association between lipid levels and the risk of ischemic stroke in women. The multivariate adjusted HR's (age, alcohol use, exercise, smoking, BMI, family history of myocardial infarction prior to age 60, current postmenopausal hormone use, history of diabetes, migraine status, cholesterol lowering medication use and randomized treatment assignments) for ischemic stroke risk with one millimole per liter-unit increase of cholesterol measures (38.7 mg/dL) were 1.17 (95% CI, 1.06-1.30) for total cholesterol and 1.15 (95% CI, 1.01-1.31) for LDL-cholesterol (Kurth et al., 2007). Studies have also reported high TG levels (Freiberg et al., 2008) and low HDL-cholesterol levels to be associated with increased risk of ischemic stroke (Tanne et al., 1997; Simons et al., 1998). A recent Swedish study, with 28 years of follw-up, including 7 400 men (aged 47-55 years) compared risk factors for CHD and stroke incidence and mortality. The study found elevated serum cholesterol levels to be an independent significant risk factor for CHD RR 1.22 (1.17-1.28), but not for stroke (Wilhelmsen et al., 2005). Similar results were found in the

Japanese collaborative cohort study (Cui et al., 2007) that examined the association between serum total cholesterol levels and the risk of CHD and stroke mortality. The study included 38 158 individuals (aged 40-79 years) and had ten years of follow-up. The multivariate adjusted (SBP, HDL-cholesterol, ethanol intake, smoking, and diabetes) OR were 3.74 (95% CI 1.11-12.6) for CHD, 0.87 (0.18-4.24) for ischemic and 0.12 (0.02-0.88) for hemorrhagic stroke for individuals with serum total cholesterol levels >=7.22 mmol/l (Cui et al., 2007).

The lipid profile in diabetic individuals is often characterized with dyslipidemia, such as elevated TG levels, preponderance of LDL-cholesterol particles and decreased levels of HDL-cholesterol (UKPDS, 1997; Betteridge, 2005). Studies have reported the diabetes related abnormal lipid profile to be more pronounced in women than in men (UKPDS, 1997; Howard et al., 1998b). Dyslipidemia is a major risk factor for CVD in diabetic individuals (Howard et al., 2000; Betteridge, 2005).

2.2.9. Other risk factors

C-reactive protein

C-reactive protein (CRP) is used as a principal inflammatory marker of systemic low-grade inflammation in research and clinical practice (Pearson et al., 2003). Elevated CRP levels have been associated with increased risk of CHD (Koenig et al., 1999) and ischemic stroke (Rost et al., 2001) in individuals without history of CVD. The Women's Health Study including 27 939 women found elevated CRP levels to better predict CVD risk comapred with elevated LDL-levels in women aged 45 years and above. The risk of cardiovascular event for women in the highest quintile of CRP (>=4.19 mg/L) was 2.3 (P<0.001) and for LDL-cholesterol 1.5 (P<0.001). The analysis were adjusted for age, smoking status, diabetes status, blood pressure, and use or nonuse of estrogen (Ridker et al., 2002). In the MONICA Ausburg Study including 936 men aged 45 to 64 years the unadjusted HR for CHD risk with 1-SD increase in the log-transformed value of CRP was 1.67 (95% CI, 1.29 to 2.17). Individuals with highest quintile of CRP (>=4.54 mg/L) had a 2.6-fold increased risk of a future coronary event (Koenig et al., 1999). Similar results were found in the Framingham Study examining the association between elevated CRP levels and the risk of ischemic stroke. The study included 591 men and 871 women without history of stroke or transient ischemic attack. The mean age of the participants was 69.7 years. Adjusting for age the RR for men in the 3rd CRP quartile (men 3.03 to 6.80 mg/L and women 3.20 to 7.31 mg/L) was 1.9 (1.04-3.61) and for women 1.8 (1.03-3.26) compared with those in the lowest quartile (Rost et al., 2001; Festa et al., 2000). Elevated CRP levels have also been associated with obesity (Yudkin et al., 1999), the metabolic syndrome (Ridker et al., 2003) and the risk of developing type 2 diabetes (Freeman et al., 2002), which have all been associated with increased risk of CVD (Wilson et al., 2002a; Johansen et al., 2003; Meeuwisse-Pasterkamp et al., 2008; Wang et al., 2007; Wang et al., 2008).

Diet

Dietary intake is a significant modifiable risk factor for CVD. In five cross-sectional population based surveys (in 1972, 1977, 1982, 1987, and 1992) in North Karelia, Kuopio and Turku in Finland it was observed that changes in nutrition such as reduction in total energy, saturated fat and cholesterol intake led to reductions in serum total cholesterol levels by 0.6 mmol/liter in both women and men (Pietinen et al., 1996). Together with increase in fruit and vegetable intake, decreased smoking among men, and improvements in blood pressure control

and other CVD risk factors contributed to a three quarters decline in CHD mortality in these areas in Finland (Vartiainen et al., 1994; Pietinen et al., 1996). The Lipid Research Clinics Prevalence Study showed a significant independent association between increased total energy intake, increased percentage of energy intake from total fat, saturated fat, and monounsaturated fat and the risk of CHD mortality among women and men aged 30-59 years. The study also found that increased percentage of energy intake from carbohydrates has a protective effect against CHD in individuals without a history of CVD (Esrey et al., 1996). A recent case-control study including 16 407 individuals from 52 countries, the INTERHEART study exmined the association between dietary patterns and the risk of acute myocardial infarction (AMI) worldwide. Three dietary patterns were identified; Oriental (with high dieatry intake of tofu, soy and other sauces), Western (dietary intake high in fried foods, salty snacks, eggs, and meat), and prudent (dietary intake high in fruit and vegetables). The study found higher levels of the prudent dietary intake to be protective against AMI. The association with Western dietary pattern and AMI was U-shaped, whereas no relationship was found between AMI and the Oriental dietary pattern. The study concluded that an unhealthy diet increases the risk of AMI and accounts for approximately 30% of the population-attributable risk of AMI worldwide (Iqbal et al, 2008). Other nutrients such as fish (Whelton et al., 2004; He et al., 2004a) and antioxidants received e.g. by fruit and vegetable intake. (Knekt et al., 1996; Huang et al., 2002; Dauchet et al., 2006) have been shown to have cardioprotective effects. The combined report from the Nurses Health Study and the Health Professionals Follow-up Study (Chiuve et al., 2008) found a significantly lower risk of stroke, escpecially ischemic stroke in individuals with a low-risk lifestyle (non-smoking, exercising daily, eating healthy diet, low alcohol intake, and normal weight during midlife) compared with individuals without a low-risk lifestyle. The study reported that in the two study populations, circa 50% of ischemic strokes could have been associated with unhealthy lifestyle factors (Chiuve et al., 2008). As for CHD, diet rich in fish (He et al., 2002; Iso et al., 2001; Fung et al., 2004; He et al., 2004b; Mozaffarian et al., 2005), fruit and vegetables (Fung et al., 2004; Dauchet et al., 2005; He et al., 2006) and whole grains (Fung et al., 2004) has been found to decrease the risk of stroke (Ding et al., 2006).

Physical activity

Low levels of physical activity is associated with increased risk of CVD (He et al., 2001). Physical inactivity often coexists with overweight and obesity (Di Pietro et al., 1998) that are associated with many CVD risk factors (Reeder et al., 1992; Wilson et al., 2002a; Field et al., 2004; Meisinger et al., 2006b) and thus with increased risk of CVD (He et al., 2001; Wilson et al., 2002a). Moderate to high levels of physical activity can reduce CVD risk substantially both in women and in men (Hu et al., 2000; Lee et al., 2003; Rothenbacher et al., 2003; Barengo et al., 2004; Hu et al., 2005a). A Finnish Study including 47 721 individuals aged 25 to 64 years found high levels of leisure time physical activity (strenuous physical activity >3 h/week) to reduce the risk of all types of stroke. The multivariate-adjusted (age, sex, area, study year, BMI, SBP, cholesterol, education, smoking, alcohol consumption, diabetes, and other two types of physical activity) HRs were 0.80 (95% CI's 0.68 to 0.93) for ischemic stroke, 0.63 (95% CI's 0.42 to 0.95) for intracerebral hemorrhage and 0.46 (95% CI's 0.27 to 0.76) for subarachnoid hemorrhage (Hu et al, 2005a). In another study from Finland with 47 840 participants aged 25–64 years moderate to high levels of occupational or leisure-time physical activity were found to decrease CHD risk both in women and in men. The multivariate adjusted (age, study year, education, alcohol consumption, and smoking status, BMI, SBP, cholesterol, and history of diabetes) HRs for high leisure-time physical activity were 0.77 (95% CI's 0.62–0.96) for women and 0.84 (95% CI's 0.74–0.95) for men

(Hu et al., 2007b). Overall CVD and all-cause mortality has been reported to decrease 2 to 17% in women and 9 to 21% in men who are moderately (light physical activity >4 h/week) or highly (strenuous physical activity >3 h/week) physically active during leisure time (Barengo et al., 2004). Furthermore, a recent exercise intervention trial study, the HERITAGE Family Study, found plasma CRP levels to decline in individuals with initially high CRP levels and sedentary lifestyles at baseline. The study included 652 subjects aged 17 to 65 years. CRP decreased 1.34 mg/L in individuals with initially high CRP levels (>3.0 mg/L) and remained the same in individuals with initially low CRP levels (<1.0mg/L) after 20 week exercise program. The results remained significant after adjusting for other risk factors; weight, glucose and insulin levels, LDL-and HDL-cholesterol, TGs, SBP and DBP and maximal oxygen intake. These results further show the effectiveness of regular physical activity in CVD prevention and treatment (Lakka et al., 2005).

Alcohol use

Moderate alcohol use has been suggested to have protective affect against development of atherosclerosis and thus CVDs. (Kannel et al., 1996; Femia et al., 2006). Moderate alcohol consumption has been reported to have cardioprotective affects (Bryson et al., 2006; Maraldi et al., 2006). The Health, Aging, and Body Composition study found a significantly lower risk of cardiac events HR 0.72 (95% CI, 0.54-0.97) in light to moderate drinkers (1 to 7 drinks per week) compared with never or occasional drinkers (Maraldi et al., 2006).

Recently the Swedish Women's Lifestyle and Health Cohort Study showed that in women under the age of 60 years who consumed moderate amounts of alcohol (20.0-69.9 g of alcohol per week) the risk of stroke was reduced to half compared with women who did not consume any alcohol (Lu et al., 2008). A meta-analysis including 35 observational studies found consumption of < 12 g of alcohol/day, to be associated with a decreased RR for total stroke, 0.83 (95%, CI, 0.75-0.91) and ischemic stroke, 0.80 (95% CI, 0.67-0.96) compared with nondrinkers. The study found a linear relationship between alcohol consumption and hemorrhagic stroke (Reynolds et al., 2003).

Low to moderate levels of alcohol use may also decrease the risk of developing type 2 diabetes mellitus (Ajani et al., 2000) and have blood pressure lowering effects (Gillman et al., 1995; Fuchs et al., 2001; Sesso et al., 2008). However, the benefit of alcohol as a CVD protective agent is U-shaped (Maraldi et al., 2006). Heavy use of alcohol both increases blood pressure (Gillman et al., 1995; Sesso et al., 2008) and the risk of CVD in men and women in long term (Lin et al., 2005; Snow et al., 2009).

Psychosocial factors

It is well known that psychosocial factors contribute to the pathogenesis of atherosclerosis and the development of CVD (De Backer et al., 2003). Depression, hopelessness and work related stress are strongly related with the formation of atherosclerosis and CVD. (Everson et al., 1997; Lynch et al., 1997; Yamanaka et al., 2005). Women are more likely to have depressive disorders than men (Gorman et al., 2006). Depression however, is a significant risk factor for CVD in both genders (Ford et al., 1998; Ferketich et al., 2000; Yamanaka et al., 2005; Surtees et al., 2008a). The United Kingdom European Prospective Investigation into Cancer-Norfolk study found a 2.7 times increased risk of ischemic heart disease in individuals with major depression compared with individuals without depression (Surtees et al., 2008a). Studies have also found an association between emotional distress (Surtees et al., 2008b),

depressive symptoms (Salaycik et al. 2007; Lee et al., 2008) and increased risk of stroke. The Baltimore Epidemiologic Catchment Area Study reported a 2.6 times increased likelihood of stroke in individuals with a history of depressive disorder (Larson et al., 2001).

CVD risk factor levels and CVD mortality is higher among men and women in lower socioeconomic groups and with lower education level. (Mackenbach et al., 2000; He et al., 2001; Yarnell et al., 2005; Metcalf et al., 2007). In the lower socioeconomic groups women and men are more often overweight (Machenbach et al., 2000; Molarius et al., 2000; Klumbiene et al., 2004; Anand et al., 2006), exercise less (Cirera et al., 1998), eat unhealthy food (Machenbach et al., 2000), are more often smokers (Cirera et al., 1998; Machenbach et al., 2000; Patja et al., 2005) and especially men consume more alcohol (Machenbach et al., 2000) compared with men and women in the higher socioeconomic groups. Studies have also reported lower socioeconomic status in childhood to be associated with CVD risk in later life (Kauhanen et al., 2006; Glymour et al., 2008). This effect has been found to be cumulative during lifecourse (Lawlor et al., 2005b).

Family history of cardiovascular disease

It is well established that the development of CVD has hereditary components (Goldstein et al., 1973; Gallagher et al., 1996; Leander et al., 2001; Lloyd-Jones et al., 2004; Nilsson et al., 2004; Murabito et al., 2005), for example the presence of apoE2 or apoE4 alleles has been found to increase the risk of CHD in men (Lahoz et al., 2001). A case control study in Stockholm Sweden, including 1 091 men and 531 women with first-time acute myocardial infarction, aged 45 to 70 years, reported adjusted OR (age, residential area, smoking, ex-smoking, job strain, physical inactivity, overweight, diabetes, hypertension, hypercholesterolemia and low socioeconomic status) for myocardial infarction to be 2.0 (95% CI, 1.6 to 2.6) in men and 2.1 (95% CI, 1.5 to 3.0) in women who had >=1 parent or sibling affected with CHD compared with men and women with no family history of CHD. The study also found synergestic interactions between family history of CHD and other known CVD risk factors, such as smoking and diabetes (Leander et al. 2001). The association between family history of stroke and increased stroke risk is not as unequivocally described as that between CHD risk and family history of CHD. The risk factor profiles for ischemic and hemorrhagic stroke subtypes were examined in a prospective observational study in Umbria, Italy including 2 395 patients with first-ever stroke incidence. The study found that 41.6% of the patients with ischemic stroke incidence had family history of stroke. For hemorrhagic stroke incidence family history of stroke was not a significant risk factor (Silvestrelli et al., 2006). In the Cohort studies of the National Survey on Circulatory Disorders, Japan, National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged (the NIPPON DATA80) including 4 640 men and 5 906 women, aged ≥30 years, no relation was found between a family history of stroke and the mortality from total stroke, cerebral infarction or intra-cerebral hemorrhage. However, the study found family history of hypertension, a known risk factor for stroke, to be correlated with increased risk of total stroke mortality among women < 60 years (HR=3.41, 95% CI; 1.49 to 7.81) and in men > 60 years (HR=1.50, 95% CI; 1.00 to 2.24) (Kadota et al., 2008).

2.3. Diabetes mellitus, intermediate hyperglcyemia and cardiovascular disease

2.3.1. Definition and classification of intermediate hyperglycemia and diabetes

Diabetes mellitus refers to a metabolic disorder that is characterized by hyperglycemia. According to WHO guidelines diabetes mellitus is defined as FPG levels >= 7.0 mmol/L and 2-h PG levels >= 11.1 mmol/L (World Health Organization/International Diabetes Federation, 2006). Two major types of diabetes exists, type 1 and type 2. The onset of type 1 diabetes can occur at any age, but it is most common in younger individuals, children and young adults. In type 1 diabetes as a result of autoimmune destruction nearly all insulin secreting β-cells in the pancreas are lost (Atkinson et al., 1994). Type 2 diabetes, which is more common in middle aged and older adults is characterized by impaired insulin secretion from β-cells of the pancreas and of peripheral insulin action (for example in fat, muscle and liver) (Prokopenko et al., 2008). In diabetic individuals disturbances in insulin secretion or peripheral insulin resistance or both further leads to disturbances in carbohydrate, fat and protein metabolism (Atkinson et al., 1994; Prokopenko et al., 2008). The gastrointestinal hormones, gastric inhibitory polypeptide and glucagon-like peptide-1 have an important role in glucose homeostasis, promoting insulin biosynthesis, insulin secretion and islet beta-cell survival (Girard 2008). The glucose-lowering actions of gastric inhibitory polypeptide are unpreserved in subjects with type 2 diabetes (Drucker et al., 2003).

The development of type 2 diabetes results from interaction between individuals genes and the environment (Ferrannini et al., 1998; Gloyn et al., 2001; Kahn, 2003; Stumvoll, 2005; Prokopenko et al., 2008). Obesity is a significant factor in the development of type 2 diabetes (National Heart Lung and Blood Institute, 1998). Mainly as a result of obesity type 2 diabetes generally results from defects in from both insulin secretion, due to β-cell dysfunction, and insulin action (Prokopenko et al., 2008). Obese older adults have substantially increased risk of developing type 2 diabetes (Chang et al., 2003; Basu et al., 2003; Villareal et al., 2008) as aging is associated with decreased insulin secretion and increased peripheral insulin resistance (Chang et al., 2003; Basu et al., 2003). However, due to increasing prevalence of obesity in children and young adults type 2 diabetes is becoming more common also in younger age groups (Rosenbloom et al., 1999; Cali et al., 2008). Type 2 diabetes is a very common, chronic disorder and accounts for > 90% of diabetes globally (Stumvoll et al., 2005).

Currently, the diagnostic criteria for type 2 diabetes has been accepted at a threshold at which micro-and macrovascular complications from diabetes become apparent. However, hyperglycemia related complications may be associated with a significantly lower threshold of glycemia than currently used for diagnosis for diabetes. Thus, two intermediate hyperglycemia categories, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (World Health Organization, 1999; World Health Organization/International Diabetes Federation, 2006), have been introduced to refer to glycemic states with increased risk of developing type 2 diabetes. (Eldstein et al., 1997; World Health Organization, 1999; Qiao et al., 2003; Ferranini et al., 2004; Li et al., 2005; World Health Organization/International Diabetes Federation, 2006). IFG and IGT refer to metabolic states between normal glucose tolerance and diabetes and are currently defined according to World Health Organization/Internation Diabetes Federation 2006 diagnostic criteria as FPG levels 6.1 to 6.9 mmol/l and 2-h PG levels <7.8 mmol/l for IFG and FPG levels <7.0 mmol/l and 2-h PG levels 7.8 to 11.1 mmol/l for IGT (**Table 1**) (World Health Organization/International Diabetes Federation, 2006).

Table 1. The World Health Organization (WHO) and International Diabetes Federation (IDF) criteria for normal glucose level, intermediate hyperglycemia and type 2 diabetes mellitus.

WHO& IDF, 2006	**Fasting plasma glucose**	**2-h plasma glucose***
Normal glucose	<6.1	<7.8
Impaired fasting glucose	>=6.1 and <6.9	<7.8
Impaired glucose tolerance	<7.0	>=7.8 and <11.1
Diabetes mellitus	>=7.0	>=11.1

*Venous plasma glucose 2-h after ingestion of 75g oral glucose load.

The intermediate states of hyperglycemia IFG and IGT represent physiologically different aspects of glucose metabolism. Fasting plasma hyperglycemia is the glucose concentration after an overnight fast and reflects abnormal hepatic glucose output and normal insulin resistance in the periphery and the liver, whereas postload hyperglycemia reflects acute increase in blood glucose level after a glucose load and is associated with decreased insulin secretion, normal to slightly reduced hepatic insulin resistance and increased insulin resistance in the periphery (especially in the skeletal muscle) (Davies et al., 2000; Unwin et al., 2002; Faerch et al., 2008).

2.3.2. Prevalence of type 2 diabetes and intermediate hyperglycemia

The incidence and prevalence of diabetes (Zimmet et al., 2001; Wild et al., 2004; Lusignan et al., 2005; International Diabetes Federation, 2006) is increasing in general public. In 2007 the number of people with diabetes in adult population was estimated to be 246 million. Based on demographic changes like urbanization by the year 2025 the number of individuals with diabetes is estimated to rise to 380 million (International Diabetes Federation, 2008). The worldwide prevalence of diabetes is similar in men and women, being somewhat higher in men under the age of 60 years and in women at advanced age. Majority of individuals with diabetes in the developed countries are over the age of 64 years and in the developing countries between 45 to 64 years (Wild et al., 2004). Individuals with diabetes generally have more CVD risk factors compared with nondiabetic individuals. For example obesity, increased blood pressure, and dyslipidemia are more common in individuals with diabetes. (Siegel et al., 1996; UKPDS, 1997).

In most populations the prevalence of IGT is higher than IFG (Harris et al., 1997; Dunstan et al., 2002; DECODE Study Group, 2003b; Rathmann et al., 2003). A gender difference has been found in the prevalence of the two glucose categories IGT being more prevalent in women and IFG in men (Dunstan et al., 2002; DECODE Study Group, 2003b; Glumer et al., 2003; Williams et al., 2003). The DECODE study (DECODE Study Group, 2003b), including 13 studies from nine European countries, reported a moderate to low prevalence of diabetes

and impaired glucose regulation in European cohorts. IGT was found to be 1.2 to 1.6 times more prevalent in women and IFG 1.2 to 2 times more prevalent in men in individuals aged 30 to 69 years. The study found the prevalence of impaired glucose regulation to increase with increasing age and to be under 15% in individuals aged 30 to 59 years and 25 to 30% in individuals over the age of 60 years in majority of the study cohorts. The increasing prevalence of impaired glucose regulation with aging resulted mainly from an increase in IGT rather than IFG in populations. In Europe diabetes was found to be undiagnosed in over 50% individuals under the age of 50 years. The prevalence of previously diagnosed diabetes was similar in both genders, however, in individuals aged > 80 years the prevalence was higher in women (DECODE Study Group, 2003b). The DECODE study group has further found that FPG and 2-h PG do not identify the same individuals and 31% of subject with diabetes remain undiagnosed if FPG alone is used for diagnosis of diabetes (DECODE Study Group, 1999).

2.3.3. Association of type 2 diabetes with coronary heart disease and stroke

Diabetes is associated with microvascular complications and diabetic individuals are at high risk of developing macrovascular diseases. CVDs account for circa two thirds of deaths in diabetic patients (Johansen et al., 2003; Meeuwisse-Pasterkamp et al., 2008). **Table 2** presents recent epidemiological studies examining the association between type 2 diabetes and CHD and stroke risk. It is estimated that most individuals with type 2 diabetes have a manifest CVD or have a greatly increased risk of a CVD event in the future (Johansen et al., 2003). Diabetes is a well-known risk factor for CHD development in both genders (Sander et al., 2003; Howard et al., 2002; Imazu et al., 2002; Natarajan et al., 2003; Hu et al., 2005b). A recent meta-analysis reported the RR for CHD mortality from diabetes for women to be 2.58 (95% CI 2.05-3.26) and for men 1.85 (1.47-2.33) (Lee et al., 2000).

The association between diabetes and increased risk of stroke is well established (Lehto et al., 1996; Tuomilehto, 1996; Wannamethee et al., 1999; Almdal et al., 2004; Kissela et al., 2005; Hu et al., 2005c; Hu et al., 2006; Mulnier et al., 2006). However, the reported magnitudes on RR vary greatly between different studies, from two to sixfold in women and from two to fourfold in men (Tuomilehto et al., 1996; Rodriquez et al., 2002; Almdahl et al., 2004; Iso et al., 2004). Type 2 diabetes is now regarded as CHD equivalent in the guidelines of National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP ATPIII) (NCEP, 2001). Even though the prevalence of diabetes increases with age, diabetes is a significant risk factor for stroke also in younger individuals (Abbott et al., 2003; Kissela et al., 2005).

Studies have reported diabetes related stroke risk to be more clearly associated with ischemic than hemorrhagic stroke rates (Karapanayiotides et al., 2004; Kissela et al., 2005). Many (Iso et al., 2004; Kissela et al., 2005; Janghorbani et al., 2007), but not all (Simons et al., 1998) studies have found a clear relationship between diabetes and ischemic stroke risk. However, studies on diabetes related hemorrhagic stroke risk have yielded conflicting results (Burchfiel et al., 1994; Jorgensen et al., 1994; Megherbi et al., 2003; Lund Håheim et al., 2006; Pham et al., 2007). In the Miyako Study including 9 651 participants (age >=40) history of diabetes was a significant risk factor for hemorrhagic stroke [HR 2.4 (95% CI 1.0- 5.8)], and total stroke [HR 2.3 (1.5- 3.5)], but not for cerebral infarction [HR 1.5 (0.8- 3.1)]. The analysis were adjusted for age, BMI, hypertension, sex, smoking, alcohol use, history of transfusion, vegetable and fruit consumption (Pham et al., 2007). The Nurses Health Study including 116 316 women (age 30-55 years) with 24 years of follow-up, found a significantly increased risk

of ischemic stroke in women with diagnosed diabetes compared with women without diabetes. However, the study found no association between diagnosed diabetes and hemorrhagic stroke risk. The multivariate adjusted (age, BMI, physical activity, menopausal status, estrogen use, smoking, hypertension, cholesterol, ischemic heart disease, aspirin use and alcohol use) RR were 2.3 (95 % CI 2.0-2.6)] for ischemic and 1.0 (95 % CI 0.7-1.4) for hemorrhagic stroke (Janghorbani et al., 2007). In the collaborative report from Honolulu Heart Study, including 7 589 Japanese-American, and the Framingham Study, with 1 216 white men, aged 45 to 68 years, diabetes (diagnosed or nonfasting serum glucose level >12.5 mmol/L after a 50-g glucose load), was associated with an increased risk of thromboembolic stroke in both Japanese-American [RR 1.9 (95% CI 1.5-2.4)] and white men [3.1 (1.6-5.8)]. Diabetes related hemorrhagic stroke risk increased in white [RR 4.5 (95% CI 1.3-15.8)], but not in Japanese-American men [RR 1.3 (0.8-2.0)]. The analysis were adjusted for age, hypertension, diabetes, total cholesterol levels, BMI, smoking, and alcohol intake (Rodriquez et al., 2002). A Swiss study, consisting of 4 064 individuals encoded in the Lausanne Stroke Registry between years 1983 and 2002, found diabetic (defined as history of diabetes or as FPG level >=7.0 mmol/L) individuals to have a lower relative prevalence of intracerebral hemorrhage [OR 0.63 (95% CI 0.45-0.9)] compared with nondiabetic individuals after multivariate adjustement for sex, age, smoking, hypercholesterolemia and hypertension (Karapathynies et al., 2004). Similarly, the European BIOMED I study found that diabetic patients were less likely to have hemorrhagic stroke than nondiabetic patients, 8.5% vs 11.5%. The study included 12 centers in 7 European countries with 4 537 patients with first ever stroke (Megherbi et al., 2003). The Copenhagen Stroke Study, including 536 men and 633 women with first ever acute stroke, found hemorrhagic stroke rates to be six times less frequent (p=0.002) in diabetic individuals compared with individuals without diabetes (Jorgensen et al., 1994).

2.3.3.1. Gender, type 2 diabetes, coronary heart disease and stroke

Several, but not all studies (Kanaya et al., 2002; Oba et al., 2008) have found diabetes to increase CHD risk more markedly in women than in men (Hu et al., 2005b; Huxley et al., 2006; Juutilainen et al., 2004). In women history of diabetes has been found to be a more significant CHD risk factor than a history of CHD, whereas in men the opposite has been observed (Natarajan et al., 2003). A recent Finnish study including 478 women and 581 men, aged 45 to 64 years, found diagnosed diabetes to be a more significant risk factor for CHD in women than in men. The multivariate adjusted HR (adjusted for smoking, BMI, SBP, total cholesterol, HDL-cholesterol, logTG) for CHD event were 9.5 (95% CI 5.4 to 16.9) in women and 2.8 (95% CI 2.1 to 3.7) in men (Juutilainen et al., 2004). In another Finnish study including 51 735 individuals, aged 25-75 years, the RR for CHD mortality (adjusted for adjusted for age, study year, BMI, SBP, total cholesterol and smoking) were 4.9 (3.8-6.2) for women and 2.1 (1.7-2.6) for men with diagnosed diabetes (Hu et al., 2005b). However, a meta-analysis including 8 prospective studies found that the stronger diabetes related RR [women 2.9 (95% CI 2.2 to 3.8) and men 2.3 (1.9 to 2.9)] for CHD was absent after adjustment for known CHD risk factor. In the study diabetes was defined by self-report, use of a diabetic medication, physician documentation in medical records, or fasting or 2-hour postchallenge glucose criteria (Kanaya et al. 2002). The DECODE study has reported similar results (Balkau et al., 2004). The Takayama Study, a recent Japanese prospective study consisting of 13 335 men and 15 724 women aged >=35 years found diagnosed diabetes to increase the risk of CHD mortality in men [RR 2.96 (95% CI 1.59 to 5.50)], but not in women [RR 0.49 (0.07 to 3.57)]. The analysis were adjusted for age, smoking, BMI, physical activity,

length of education, history of hypertension, total energy intake and intake of vegetables, fat and alcohol (Oba et al., 2008).

Several studies have found greater diabetes related stroke risk in diabetic women compared with diabetic men (Lehto et al., 1996; Tuomilehto et al., 1996; Har et al., 2000; Almdal et al., 2004; Iso et al., 2004). The Copenhagen City Heart Study found a 2- to 6.5-fold increased risk of stroke in diabetic women and 1.5- to 2-fold in diabetic men compared with individuals without diabetes . The analysis were adjusted for tobacco consumption, physical activity alcohol consumption, BMI, TGs and total cholesterol levels. The study included 13 105 subjects, aged 55 to 64 years, and had a 20 year follow-up (Almdal et al., 2004). Similar results have been found in two Finnish studies that found the diabetes-related stroke risk to be more marked in women than in men (Lehto et al., 1996; Tuomilehto et al., 1996). A study including 1 059 diabetic men and women and 1 373 nondiabetic control subjects, aged 45 to 64 years, from Eastern and Western Finland, found diabetic men to have a two to threefold greater and diabetic women a fivefold greater risk of stroke compared with non-diabetic individuals (in men: OR 2.4 [95% CI, 1.2 to 4.9] in East Finland and 3.3 [1.6 to 6.9] in West Finland, in women: OR 5.5 [2.4 to 12.9] in East Finland and 5.4 [2.3 to 12.6] in West Finland) (Lehto et al., 1996). Another prospective study (mean follow-up 16.4 years) from Eastern Finland, including 8 077 men and 8 572 women, found 16% of stroke deaths to be related to diabetes in men and 33% in women (Tuomilehto et al., 1996). Increased diabetes-related stroke risk was also reported in the Renfrew-Paisley Study. The multivariate adjusted RR for stroke mortality were 2.89 (95% CI 1.49-5.62) for men and 3.98 (2.29-6.91) for women. The study included 7 052 men and 8 354 women, aged 45 to 64 years (Hart et al., 2000).

Table 2. Relative risk (95% CI) coronary heart disease (CHD) and stroke in relation to diabetes as compared with non-diabetics in recent prospective studies.

Study	Follow-up (yrs)	Diabetes definition	Population, age (yrs)	CHD mortality/ event	Overall stroke incidence /mortality	Ischemic stroke incidence /mortality	Hemorrhagic stroke incidence /mortality	Reference
North Karelia and Kuopio cohorts	16.4 (mean)	diagnosed diabetes	8 572 women 8 077 men, age 30 to 59		women 4.89 (2.83-8.45) men 3.35 (1.96-5.73)			Tuomilehto et al., 1996
The Honolulu Heart Study and The Framingham Study	20	non-fasting serum glucose after a 50-g load or history of non-fasting levels	7 589 Japanese-American men 1 216 white men, age 45 to 68			Japanese-American 1.9 (1.5-2.4) white 3.1 (1.6-5.8)	Japanese-American 1.3 (0.8-2.0) white 4.5 (1.3-15.8)	Rodriguez et al., 2002
The Framingham Heart Study and the Framingham Offspring Study	20	fasting plasma glucose, plasma glucose or diagnosed diabetes	2 749 women 2 494 men, age 35-74	women 3.8 (2.2-6.6) men 2.1 (1.3-3.3)				Natarajan et al., 2003
The Copenhagen City Heart Study	20	non-fasting plasma glucose or diagnosed diabetes	7 198 women 5 907 men, age >=20	women 1.5-4.5 men 1.5-2.0	women 2.0-6.5 men 1.5-2.0			Almdal et al., 2004

Five Japanese study cohorts	17	fasting or non-fasting serum glucose, diagnosed diabetes	6 295 women 4 287 men, age 40-69			women 2.2 (1.2–4.0) men 1.8 (1.0–3.2)		Iso et al., 2004
Finnish study cohort	13	diagnosed diabetes	478 women 581 men, age 45-64	women 9.5 (5.4 -16.9) men 2.8 (2.1- 3.7)				Juutilainen et al., 2004
Finnish study cohort	17.2 (mean)	diagnosed diabetes	26 520 women 25 215 men, age 25-75	women 4.9 (3.8-6.2) men 2.1 (1.7-2.6)				Hu et al., 2005b
The Nurses Health Study	26	diagnosed diabetes	116 316 women, age 30–55		1.8 (1.7–2.0)	2.3 (2.0–2.6)	1.0 (0.7–1.4)	Janghorbani et al., 2007
The Miyako Study	13.8 (mean)	diagnosed diabetes	5 397 women 4 254 men, age >=40		2.3 (1.5- 3.5)	1.5 (0.8- 3.1)	2.4 (1.0- 5.8)	Pham et al., 2007
Takayama Study	7	diagnosed diabetes	15 724 women 13 335 men, age >=35	women 0.5 (0.1 -3.6) men 3.0 (1.5 - 5.5)				Oba et al., 2008

2.3.4. Association of intermediate hyperglycemia with coronary heart disease and stroke

Diabetes is a well known risk factor for CVD (Tuomilehto et al. 1996; Lowe et al., 1997; Natarajan et al., 2003; Hu et al., 2005b). **Table 3** presents recent epidemiological studies examining the association between hyperglycemia and CHD and stroke risk. Hyperglycemia is associated with many CVD risk factors (Glumer et al., 2003) and some, but not all (Qureshi et al., 1998) studies have reported elevated glucose levels to predict CVD incidence also in nondiabetic individuals (Perry et al., 1994; Balkau et al., 1998; de Vegt et al., 1999; Coutinho et al., 1999; DECODE Study Group, 2003a; Levitan et al., 2004; Lawlor et al., 2007). A recent overview of epidemiological studies and surveys from 52 countries found 21 % of deaths from ischemic heart disease and 13% of stroke deaths to be associated with higher than optimum blood glucose levels (Danaei et al., 2006). Other studies have found similar results (Balkau et al. 1998; The DECODE Study Group, 2001). In a pooled analysis from three cohort studies with non-diabetic men, the Whitehall Study (10 025 men), the Paris Prospective study (6 629 men) and the Helsinki Policemen Study (631 men) a significantly increased risk of CHD mortality was found in the top 2.5% of 2-h blood glucose distribution (Balkau et al., 1998). However, not all studies have confirmed these findings. The Third National Health and Nutrition Examination survey (from 1988 to 1994) in the United States found no association between hyperglycemia (defined by FPG >140 mg/dl or 2-h PG >200 mg/dl) and the incidence of myocardial infarction. The multivariate adjusted (age, sex, education, race/ethnicity, hypertension, cholesterol, BMI, smoking) OR was 0.9 (95% CI 0.5-1.6). The study included 6 547 participants aged 40 to 74 years (Qureshi et al., 1998).

The association between hyperglycemia and increased risk of stroke in diabetic individuals is well established (Håheim et al., 1995; Fuller et al., 2001). However, studies have provided conflicting results regarding the association between hyperglycemia and risk of stroke in nondiabetic individuals (Håheim et al., 1995; Qureshi et al., 1998; Wannamethee et al., 1999; Hart et al., 1999). As for CHD incidence the Third National Health and Nutrition Examination survey (above) found no association between stroke incidence and impaired glucose tolerance (defined by FPG or 2-h PG levels) in individuals without diabetes. The multivariate adjusted OR for stroke incidence was 0.9 (95% CI 0.5-1.6) (Qureshi et al., 1998). Similar findings were obtained in the Oslo Study (Håheim et al., 1995). The RR (adjusted for age) for stroke incidence was 1.02 (95% CI 0.83 to 1.26) in men without diabetes. The study included 16 209 men aged 40 to 49 years and had 18-years of follow-up (Håheim et al., 1995). In the Honolulu Heart Program, including 7 549 Japanese-American men aged 45 to 68 years an increased risk of thromboembolic [RR (adjustment age, BMI, hypertension, left ventricular hypertrophy, cholesterol, TGs, uric acid, hematocrit, smoking alcohol use, physical activity index) 1.43 (95% CI 1.00-2.04)], but not hemorrhagic stroke [0.96 (0.51-1.82)] was found with high serum glucose levels (>=225 mg/dl) defined by 1-h postload glucose measurement compared with indivduals with normal glucose levels (<151 mg/dl). The study had a 22-year follow-up (Burchfiel et al., 1994). In a more recent study, the Turku Elderly Study, with 1 032 indivduals aged 70 years individuals with IGT (defined by 2-h plasma glucose levels between 7.80 and 11.09 mmol/l) had more stroke incidences compared with normal group, but the difference was not statistically significant (Kaarisalo et al., 2006). The association between hyperglycemia and stroke events is thus less clearly established than that between hyperglycemia and CHD. However, a clear correlation has been found between hyperglycemia and stroke outcome. It has been found that both individuals with and without

diabetes have worsened stroke outcome with admission hyperglycemia (Moulin et al., 1997; Capes et al., 2001). Impaired glucose tolerance has also been found to increase stroke recurrence in patients with transient ischemic attack or minor ischemic stroke (Vermeer et al., 2006).

2.3.4.1. Gender, intermediate hyperglycemia, coronary heart disease and stroke

Several studies have examined the gender-related risk on CHD and stroke in diabetic individuals (Kanaya et al., 2002; Lehto et al., 1996; Tuomilehto et al. 1996; Hart et al., 2000; Oba et al., 2008; Juutilainen et al., 2004; Hu et al., 2005b; Huxley et al., 2006). However, data on gender related risk on CHD and stroke in individuals with hyperglycemia without diabetes is scarce. The Chicago Heart Association Detection Project in Industry including 19 502 men and 7 251 women, examined the association between 1-h postload plasma glucose levels at baseline and 22-year CHD mortality in different age groups. The study found a clear relationship between increased risk of CHD and elevated glucose levels in both genders. The multivariate adjusted RR were 1.07 (95% CI 1.01-1.14) and 1.03 (0.93-1.13) in men and 1.14 (1.01-1.28) and 1.18 (1.03-1.34) in women aged 40-59 and 60-74 years, respectively (Orencia et al. 1997). The Asia Pacific Cohort Study collaboration, including 237 468 participants, found a 23% decreased risk of of ischemic heart disease for each 1 mmol/l reduction in fasting glucose levels in individuals without diabetes in women and men across all age groups (Lawes et al., 2004). The DECODE Study (2001) including 15 388 men and 7 126 women, aged 30-89 years, from 10 European cohorts, found IGT to increase CHD risk in men, but not in women. IFG was not found to predict CHD mortality in neither gender. The multivariate adjusted (age, study, total cholesterol, BMI, SBP, smoking) HRs were 1.05 (95% CI 0.80-1.37) and 1.29 (1.02-1.64) in men and 1.25 (0.39-4.03) and 1.22 (0.69-2.15) in women for FPG and 2-h PG, respectively. The median follow-up length for the study was 8.8 years (The DECODE Study Group, 2001).

Few studies have examined the gender difference in risk of stroke related to hyperglycemia in individuals without diabetes. The Chicago Heart Association Detection Project in Industry examined the association with 1- hour postload plasma glucose levels and the risk of stroke in 19 502 men and 7 251 women. The study found a significant association between elevated glucose levels and stroke mortality in men only. The multivariate adjusted (age, race, education, SBP, smoking, serum cholesterol, BMI and ECG abnormalities) hazard ratio were 1.01 (0.80-1.27) and 1.17 (0.92-1.48) in women and men 1.19 (1.05-1.35) and 1.23 (1.02-1.49) aged 40 to 59 and 60 to 74, respectively. The study had a 22 -year follow-up (Orencia et al., 1997). In contrast, the Renfrew/Paisley study, including 7 052 men and 8 354 women, aged 45 to 64 years, found elevated (top 5%) nonfasting blood glucose levels to be associated with 20-year stroke mortality in nondiabetic women [OR 2.17 (95% CI 1.44-3.25)], but not in nondiabetic men [1.39 (0.79-2.42)]. The analysis were adjusted for age, SBP, DBP, smoking, adjusted forced expiratory volume in 1 second, cardiothoracic ratio, height, BMI, diabetes and preexisting CHD (Hart et al., 1999).

Table 3. Relative risk (95% CI) of coronary heart disease (CHD) and stroke in relation to increase in glucose levels (mmol/L) or as indicated.

Study	Follow-up (yrs)	Glucose definition	Population, age (yrs)	CHD mortality/event	Overall stroke incidence /mortality	Ischemic stroke incidence /mortality	Hemorrhagic stroke incidence /mortality	Reference
The Honolulu Heart Program	22	non-fasting glucose 1-hour after a 50-g load, high normal compared with low normal	7 549 men, age 45 to 68			1.43 (1.00-2.04)	0.96 (0.51-1.82)	Burchfiel et al.,1994
The British Regional Heart Study	9.5	non-fasting blood glucose, upper quintile compared with all the lower quintiles	7 735 men, age 40 to 59	1.5 (1.1-2.6)				Perry et al.,1994
Oslo Study	18	non-fasting serum glucose	16 209 men, age 40 to 49		1.02 (0.83-1.26)			Håheim et al.,1995

Chicago Heart Association Detection Project in Industry	22	1-hour postload plasma glucose, 40mg/dl increase	10 269 men, age 18 to 39 6 319 women 7 993 men, age 40 to 59 932 women 1 240 men, age 60 to 74	*age 18 to 39* men 1.06 (0.91-1.24) *age 40 to 59* women 1.14 (1.01-1.28) men 1.07 (1.01-1.14) *age 60 to 74* women 1.18 (1.03-1.34) men 1.03 (0.93-1.13)	*age 40 to 59* women 1.01 (0.80-1.27) men 1.19 (1.05-1.35) *age 60 to 74* women 1.17 (0.92-1.48) men 1.23 (1.02-1.49)		Orencia et al.,1997
Whitehall Study, the Paris Prospective study and the Helsinki Policemen Study	20	fasting plasma glucose, 2-h postload plasma glucose, the top 2.5 % of glucose level	17 285 men, age 45 to 55	1.34 (1.00-1.80)			Balkau et al.,1998

NHANES III, Third National Health and Nutrition Examination Survey		fasting plasma glucose, 2-h postload plasma glucose, impaired glucose tolerance compared with normal glucose tolerance	6 547 individuals, age 40 to 74	Odds ratio 1.1 (0.7 -1.6)	Odds ratio 0.9 (0.5-1.6)	Qureshi et al.,1998
Renfrew/ Paisley general population study	20	non-fasting blood glucose, the top 5% compared with the rest	8 353 women 7 058 men, age 45 to 64		women 3.98 (2.29-6.91) men 2.89 (1.49-5.62)	Hart et al., 1999
Honolulu Heart Program	23	non-fasting state 1 h after a 50-g glucose load, asymptomatic hyperglycemia compared with low normal	8 006 Japanese-American men, age 45-68	2.01 (1.44-2.81)		Rodriguez et al.,1999

The DECODE study	8.8	fasting plasma glucose, 2-h plasma glucose	7 126 women 15 388 men, age 30 to 89	FPG: women 1.25 (0.39-4.03) men 1.05 (0.80-1.37) 2-h PG: women 1.22 (0.69-2.15) men 1.29 (1.02-1.64)	FPG: women 3.02 (1.11-8.21) men 0.89 (0.57-1.38) 2-h PG: 1.21 (0.56-2.59) men 1.26 (0.84-1.88)	The DECODE Study Group, 2001
The Turku Elderly Study	9.6 (mean)	2-h plasma glucose, impaired glucose tolerance	1 032 individuals, age 70		1.47 (0.83-2.61)	Kaarisalo et al.,2006

3 AIMS OF THE STUDY

1. To compare the fasting plasma glucose and 2-h plasma glucose criteria with regard to their relation to stroke mortality in European women and men (Article I).

2. To compare between fasting and 2-h plasma glucose criteria in their relation to incidence of ischemic and hemorrhagic stroke (Article II).

3. To study the age-and gender-difference in incidence of coronary heart disease and ischemic stroke and to estimate to what extent the known cardiovascular risk factors have attributed to the difference (Article III).

4. To assess age- and gender-difference in the diabetes-related risk of coronary heart disease and ischemic stroke (Article IV).

4 POPULATIONS AND METHODS

4.1. Study population

The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) was first undertaken on the initiative of the European Diabetes Epidemiology Study Group in 1997 with the aim to evaluate the new diagnostic criteria for diabetes proposed by the American Diabetes Association in 1997. Researchers in Europe who had done population-based or large occupational studies on the prevalence of diabetes mellitus applying standard 2-hour 75g oral glucose tolerance tests were invited to participate. The study consists of 31 European cohorts from 14 European countries (Cyprus, Denmark, Finland, France, Iceland, Israel, Italy, Malta, the Netherlands, Poland, Spain, Sweden, Turkey, United Kingdom). All the individuals included in the study had FPG and 2-h PG (after 75 g of glucose load) values at baseline, and most of the cohorts were followed up with regard to the mortality and morbidity. Individual data from different participating European cohorts were sent to the Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, in Helsinki, Finland for data analyses. Each study had been approved by the local Ethics Committees and the Ethics Committee of the National Institute for Health and Welfare approved the data analysis plan. This is a sub-data analysis of the DECODE study including 25 181 individuals, 11 844 (47%) men and 13 345 (53%) women, from 14 European cohorts. The characteristics of subjects are shown in **Table 4**.

4.1.1. Study population in articles I-IV

Article I The study population comprised of 21 706 individuals, 11 844 men and 9 862 women, aged 25 to 90 years, from 13 European DECODE cohorts. The maximum length of follow-up ranged from 3.8 to 27.9 years among different cohorts. Measurements for fasting plasma glucose and 75g 2-h oral glucose tolerance test, BMI, total serum cholesterol, systolic and diastolic blood pressure, antihypertensive treatment, and smoking status were available for all individuals included in the study.

Article II Only subjects without a history of CVD were included in the study. The study population comprised of 18 360 individuals, 9 985 men and 8 375 women, aged 25 to 90 years, from 9 DECODE cohorts from Finland and Sweden. The maximum length of follow-up ranged from 3.8 to 27.9 years among different cohorts. Measurements for fasting plasma glucose and 75g 2-h oral glucose tolerance test, BMI, total serum cholesterol, systolic and diastolic blood pressure, antihypertensive treatment, and smoking status were available for all individuals included in the study.

Articles III-IV Only subjects without a history of CVD were included in the study. The study population comprised of 9 278 participants, 5 111 women and 4 167 men, aged 40 to 69 years, from 7 cohorts from Finland and Sweden. The maximum length of follow-up ranged from 4.9 to 20.6 years in women and in men. A total of 384 (7.5%) women and 442 (10.6%) men had diabetes (both diagnosed and undiagnosed). Measurements for fasting plasma glucose and 75g 2-h oral glucose tolerance test, BMI, total serum cholesterol, HDL-cholesterol, systolic and diastolic blood pressure, antihypertensive treatment, and smoking status were available for all individuals included in the study.

Table 4. Charasteristics of the study population at baseline according to study cohort.

	Men, (No)	Women, (No)	Age	Body mass index (Kg/m^2)	Cholesterol (mmol/L)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Fasting plasma glucose (mmol/l)	2-h plasma glucose (mmol/l)	Known DM, No (%)	Smoking, No (%)
Finland, East-West[†]	405		76.2 (4.5)	26.4 (3.8)	5.74 (1.13)	157 (22)	85 (11)	5.7 (0.8)	7.5 (2.6)	51 (12.6)	56 (13.8
FINRISK-1987	1261	1440	54.0 (5.8)	27.8 (4.3)	6.44 (1.23)	148 (21)	88 (11)	5.2 (0.7)	6.3 (2.0)	89 (3.3)	510 (18.9)
FINRISK-1992	877	1041	54.1 (6.0)	27.5 (4.3)	5.96 (1.05)	144 (20)	86 (12)	5.5 (0.8)	6.2 (2.2)	69 (3.6)	390 (20.3)
FINRISK-2002	1786	2055	57.9 (7.8)	27.9 (4.6)	5.78 (1.03)	144 (21)	82 (11)	5.8 (0.9)	6.8 (2.6)	267 (7.0)	1083 (28.2)
Helsinki Policemen Study[†]	1136		44.7 (8.0)	25.7 (2.8)	6.14 (1.24)	138 (18)	83 (11)	6.0 (0.7)	5.5 (1.6)	16 (1.4)	552 (48.6)
Vantaa	271	335	65.2 (0.4)	27.2 (4.3)	6.06 (1.08)	151 (20)	87 (10)	5.5 (0.7)	7.5 (2.0)	58 (9.6)	101 (16.7)
Italy, Cremona	799	1003	58.4 (10.8)	26.6 (4.4)	6.12 (1.13)	145 (21)	80 (12)	5.1 (0.8)	5.6 (2.3)	140 (7.8)	399 (22.1)
Malmö Preventive Project		3483	54.8 (2.4)	25.6 (4.5)	6.13 (1.08)	127 (17)	82 (9)	6.1 (0.9)	8.7 (2.2)	3469 (14)	1002 (28.8)
The Netherlands, Hoorn Study	1087	1282	61.7 (7.3)	26.6 (3.6)	6.66 (1.18)	135 (20)	82 (10)	5.6 (1.0)	6.0 (2.9)	81 (3.4)	790 (33.3)
Zuthpen Study[†]	479		75.8 (4.5)	25.6 (3.1)	6.09 (1.10)	150 (22)	82 (12)	5.8 (1.0)	6.5 (3.0)	37 (7.7)	109 (22.8)
Sweden, MONICA	1733	1760	48.9 (13.4)	26.1 (4.3)	6.05 (1.29)	129 (20)	80 (11)	5.2 (0.7)	5.7 (2.9)	304 (8.7)	654 (18.7)
Uppsala[†]	1164		71.0 (0.6)	26.3 (3.4)	5.82 (0.99)	147 (19)	84 (9)	5.5 (0.9)	7.6 (2.9)	67 (5.8)	243 (20.9)
U.K., Goodinge	448	570	54.6 (10.3)	25.8 (4.8)	6.45 (1.31)	119 (21)	70 (12)	6.1 (0.9)	6.3 (2.2)		385 (37.8)
Newcastle	398	376	54.8 (12.5)	26.4 (4.5)	5.84 (1.15)	131 (23)	75 (13)	5.9 (1.1)	6.5 (2.6)	17 (2.2)	216 (27.9)

Data are given as means (standard deviation) adjusted for age, study and sex, or as number (%) as noted

[†] The study includes only men

4.2. Methods

4.2.1. Baseline measurements

From each participating study crude data on, date of baseline examination, gender, age, height, weight, status of known diabetes and information on how diabetes was assessed, time of day of blood sampling, blood sampling used (venous whole blood, venous plasma, capillary whole blood), glucose load; FPG (mmol/L) ≥10 hours fasting time , and 2-h PG (mmol/L) 2-h after 75-g glucose load, total serum cholesterol (mmol/L), SBP (mmHg) and DBP (mmHg), antihypertensive treatment, and smoking status were collected and the details are shown in Appendix 1., Appendix 2. and Appendix 3. Vital status and the cause of death were recorded for participants in all of the studies. Participants who had emigrated and whose vital status could not be confirmed were treated as censored cases.

4.2.2. Definitions

Diabetes and intermediate hyperglycemia

Individuals with history of diabetes were classified with known diabetes. Individuals who had not been diagnosed previously with diabetes were classified according to either 2-h PG criteria ≥11.1 mmol/L for newly diagnosed diabetes, 7.8-11.0 mmol/L for IGT, and <7.8 mmol/L for normal glucose tolerance (NGT)) or FPG criteria ≥7.0 mmol/L for newly diagnosed diabetes, 6.1-6.9 mmol/L for IFG, and <6.1 mmol/L for normal fasting glucose (NFG) (World Health Organization and International Diabetes Federation, 2006) criteria. IFG and IGT refer to states of intermediate hyperglycemia.

Cardiovascular disease events

The fatal and nonfatal events of CHD and cerebrovascular diseases were coded according to the International Classification of Diseases (8^{th}, 9^{th} revisions and 10^{th} revision). The nonfatal CHD events were classified with codes 410-411 (ICD-9) and I21-I22, I24 (ICD-10) and fatal events with codes 410-414 (ICD-9) and I20-I25 (ICD-10). Fatal events of cerebrovascular diseases were coded with 430-439 (ICD-8 and ICD-9) and I60-I69 (ICD-10). Nonfatal and fatal events for overall stroke were classified with codes 430-431, 433-434, 436 (ICD-9) and I60-I61, I63-I64 (ICD-10) and the nonfatal and fatal events for subtypes of stroke with codes 433-434 (ICD-9) and I63 (ICD-10) for ischemic stroke, with codes 430-431 (ICD-9) and I 60-I61 (ICD-10) for hemorrhagic stroke and with codes 436 (ICD-9) and I64 (ICD-10) for unspecified stroke. In the Finnish and Swedish cohorts the information on CVD mortality and morbidity were collected from National Causes of Death Register and the National Hospital Discharge Registry and ascertained by using a computerized record linkage of individual ID numbers of each of the individuals participating in the study.

Other measurments

The BMI was calculated as weight in kilograms divided by the square of height in meters, mean arterial pressure (MAP) was defined as [(2 x diastolic)+systolic] / 3). Individuals were classified with hypertension if SBP ≥140 and/or DBP ≥ 90 mmHg and/or they had hypertension treatment. Smoking status was defined as non-smoker, ex-smoker or current smoker.

4.2.3. Statistical Methods

The data analysis was carried out by using SPSS for Windows version 15.0. Cox proportional hazards model was used to estimate the assocation between risk factors with the end points. The analysis was adjusted for age, center, MAP or hypertension status, BMI, total serum cholesterol, HDL-cholesterol, smoking status and sex. General linear model of the univariate analysis of variance was used to estimate the means. Chi-squared log-likelihood ratio test were used to evaluate whether the two glucose criteria differ in their prediction of the new events of stroke. Univariate analysis of variance was used to estimate the trend in cardiovascular risk factors with aging. A p-value <0.05 (two-tailed) was considered statistically significant.

The equations for transformation of glucose concentration was done based on 294 paired blood samples of whole (capillary and serum) blood and plasma glucose concentration drawn from a standard 75 g oral glucose tolerance test in 74 subjects at 0, 30, 60 and 120 minutes at at the Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki Finland. A mixed model with random effects of individual and sample was used to evaluate the relationship between glucose concentrations measured by different measures (Carstensen et al., 2008).

The transformation of glucose concentration:

- plasma glucose (mmol/l) =0.558+1.119 * whole blood glucose (mmol/l)
- plasma glucose (mmol/l) =0.102+1.066 * capillary blood glucose (mmol/l)
- plasma glucose (mmol/l) =-0.137+1.047 * serum glucose (mmol/l)

5 RESULTS

5.1. Hyperglycemia and stroke incidence and mortality

- fasting versus 2-hour glucose criteria (Article I, II)

5.1.1. Charasteristics of paricipants

Baseline characteristics of subjects (Article I, II) are shown in **Table 5**. Both women and men with diagnosed and undiagnosed diabetes were older and had higher BMI compared to individuals without diabetes.

Table 5. Baseline characteristics and multivariate adjusted hazard ratios (95 % confidence intervals) for death from stroke for subjects according to fasting (FPG) and 2-hour plasma (2-h PG) glucose categories.

	FPG (mmol/L)			*2-h PG (mmol/L)*			*Known DM*
	< 6.1	*6.1-6.9*	*≥ 7.0*	*< 7.8*	*7.8-11.0*	*≥11.1*	
Men							
No. (%)	8540 (72.1)	2043 (17.2)	537 (4.5)	9065 (76.5)	1558 (13.2)	497 (4.2)	724 (6.1)
Age	56.9 (0.1)	57.2 (0.3)	62.4 (0.5)	55.8 (0.1)	63.2 (0.3)	65.1 (0.5)	62.8 (0.4)
Body mass index (Kg/m^2)	26.3 (0.0)	27.4 (0.1)	29.0 (0.2)	26.3 (0.0)	27.7 (0.1)	28.9 (0.2)	28.3 (0.1)
Cholesterol (mmol/L)	6.04 (0.01)	6.09 (0.03)	6.11 (0.05)	6.07 (0.01)	5.99 (0.03)	6.04 (0.05)	5.78 (0.04)
Systolic blood pressure (mmHg)	140 (0.2)	145 (0.4)	148 (0.9)	140 (0.2)	147 (0.5)	151 (0.9)	145 (0.7)
Diastolic blood pressure (mmHg)	83 (0.1)	85 (0.3)	87 (0.5)	83 (0.1)	86 (0.3)	87 (0.5)	84 (0.4)
Smoking, No (%)	2507 (29.4)	637 (31.2)	157 (29.2)	2835 (31.3)	360 (23.1)	106 (21.3)	166 (22.9)
Stroke							
No (%)	141 (1.7)	45 (2.2)	15 (2.8)	153 (1.7)	35 (2.2)	13 (2.6)	30 (4.1)
No/1000 Person-years	1.46	1.90	3.24	1.43	2.47	3.50	5.57
Women							
No. (%)	8169 (82.8)	969 (9.8)	252 (2.6)	7766 (78.7)	1281 (13.0)	343 (3.5)	472 (4.8)
Age	54.9 (0.1)	59.0 (0.3)	61.1 (0.6)	54.5 (0.1)	59.6 (0.3)	62.4 (0.5)	60.8 (0.5)
Body mass index (Kg/m^2)	26.5 (0.1)	28.6 (0.2)	30.6 (0.3)	26.4 (0.1)	28.6 (0.1)	30.0 (0.3)	30.1 (0.2)

Cholesterol (mmol/L)	6.22 (0.01)	6.27 (0.04)	6.32 (0.07)	6.22 (0.01)	6.27 (0.03)	6.21 (0.06)	5.86 (0.05)
Systolic blood Pressure (mmHg)	137 (0.2)	141 (0.7)	143 (1.3)	137 (0.2)	144 (0.6)	147(1.1)	147(1.0)
Diastolic blood pressure (mmHg)	80 (0.1)	81 (0.4)	82 (0.7)	80 (0.1)	83 (0.3)	84 (0.6)	81 (0.5)
Smoking, No (%)	1650 (20.2)	237 (24.5)	67 (26.6)	1712 (22.0)	184 (14.4)	58 (16.9)	67 (14.2)
Stroke							
No (%)	37 (0.5)	10 (1.0)	7 (2.8)	36 (0.5)	9 (0.7)	9 (2.6)	14 (3.0)
No/1000 Person-years	0.44	1.25	3.35	0.46	0.72	3.03	3.93

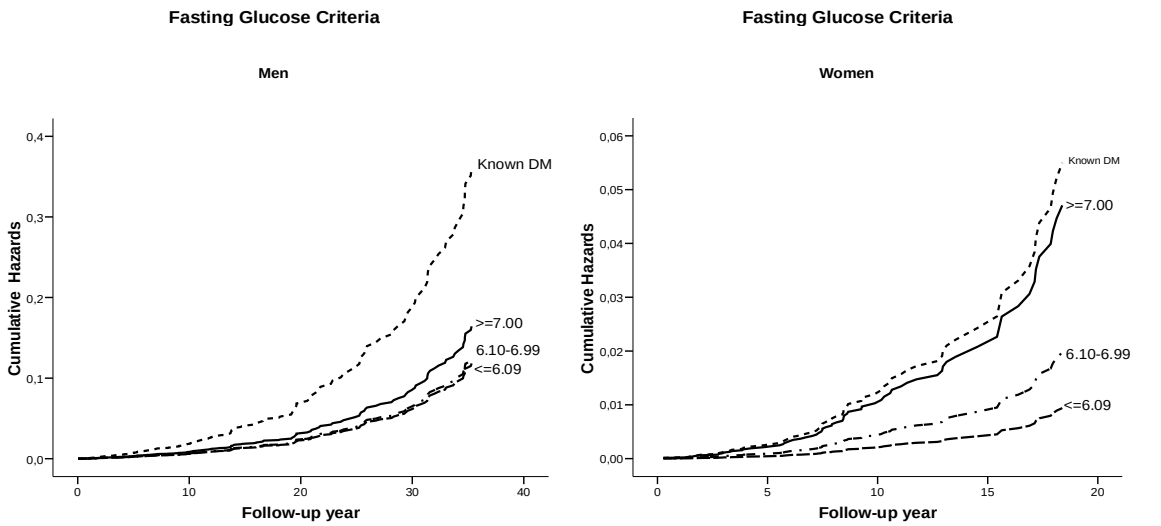
Data are given as means (standard error) adjusted for age, and study or as number (%) as noted.

5.1.2. Hyperglycemia and stroke mortality (Article I)

Diagnosed diabetes increased stroke mortality in both genders. The multivariate-adjusted hazard ratio (adjusted for age, study, hypertension status, total cholesterol, BMI and smoking) for fatal stroke events was highest in men and women with screen detected diabetes defined by either FPG or 2-h PG criteria as compared with men and women with normal or impaired glucose values. The cumulative hazard ratios for stroke mortality were highest in individuals with diagnosed diabetes and screened diabetes defined by either glucose criteria (**Figure 2a-2d**); in women the risk was slightly increased for IFG (**Figure 2b**) and in men for IGT (**Figure 2c**). The stroke mortality risk was lowest in women with NGT or IGT (**Figure 2d**) and in men with NFG or IFG (**Figure 2a**).

a

b



c

d

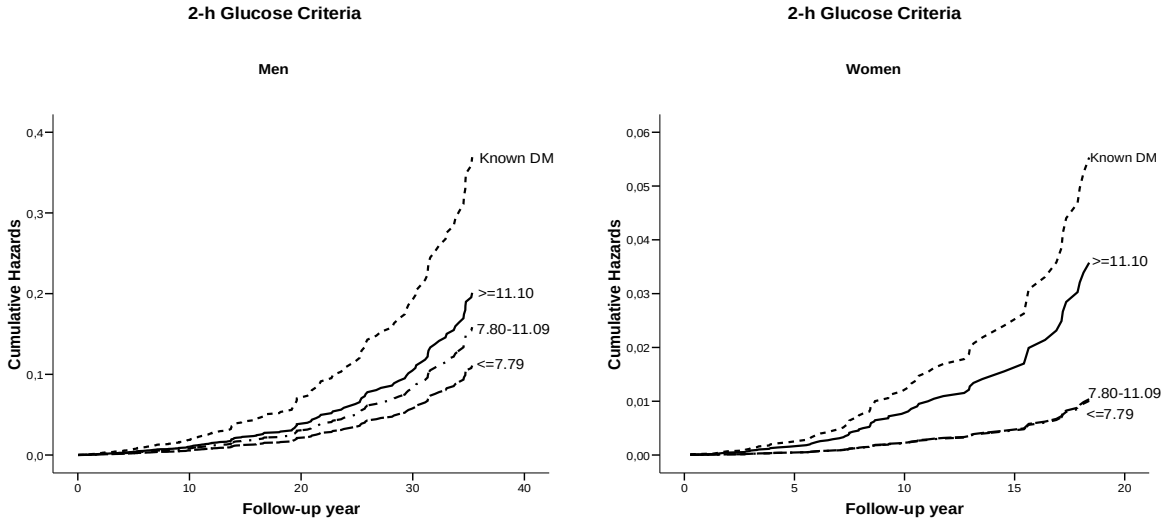


Figure 2. Cumulative stroke mortality curves derived from Cox regression analysis for FPG (mmol/l) and 2-h PG category and for people with prior history of diabetes (known DM) in men (**Figure 2a-2c**) and in women (**Figure 2b-2d**). The analysis is adjusted for age, study, BMI, total cholesterol, smoking and hypertension status.

The hazard ratios corresponding to 1 SD increase in 2-h PG were a better predictor of a fatal stroke event than those in FPG in men [1.21 (1.06-1.38)] vs 1.04 (0.85-1.27)], whereas FPG was better than 2-h PG in women [1.31 (1.07-1.61) vs 1.54 (1.26-1.90)], after adjusting for age, study, BMI and total cholesterol. Addition of 2-h PG to the model with FPG significantly improved prediction of stroke mortality in men (Chi square = 10.12, p = 0.001) but not in women (Chi square = 0.01, p = 0.94), whereas addition of FPG with 2-h PG improved stroke mortality in women (Chi square = 4.08, p = 0.04), but not in men (Chi square = 3.29, p = 0.07). The interaction between gender and stroke mortality was statistically significant for FPG (p=0.05), but not for 2-h PG (p= 0.53) levels.

5.1.3. Hyperglycemia and the incidence of ischemic and hemorrhagic stroke (Article II)

Both FPG and 2-h PG predicted the risk of ischemic and overall stroke, but not hemorrhagic stroke subtype. The multivariate-adjusted hazard ratios corresponding to a 1 SD increase for ischemic stroke were 1.12 (1.02-1.22) and 1.14 (1.05-1.24) and for hemorrhagic stroke 1.07 (0.88-1.30) and 1.06 (0.90-1.27) for FPG and 2-h PG, respectively after adjustment for age, study, BMI, total cholesterol, smoking, MAP and sex. Adding 2-h PG to the model with FPG significantly improved the prediction of stroke incidence of all stroke subtypes (χ^2 = 4.93, p=0.03) and for ischemic stroke (χ^2 =5.45, p=0.02) whereas adding FPG to the model with 2-h PG did not improve the prediction of stroke incidence neither for all stroke subtypes (χ^2 =0.79, p=0.37) nor for ischemic stroke (χ^2 = 0.02, p=0.88). The linear form of the FPG and 2-h PG did not predict the incidence of hemorrhagic stroke (**Table 6**). We also performed a sensitivity analysis in which the length of follow-up was truncated at 15 years. The present findings were in accordance with the results we obtained from the sensitivity analysis. The hazard ratios for FPG (**Figure 3a)** and 2-h PG (**Figure 3b**) for each study cohort and for all cohorts combined based on the meta-analysis showed no large variation in between the study cohorts with regard to the relationship between hyperglycemia and stroke incidence (Data not published).

Table 6. Hazard ratios (95 % confidence intervals) for the incidence of overall and subtypes of stroke corresponding to a 1SD increase in fasting (FPG) and 2-hour plasma glucose (2-h PG) levels (mmol/L). The χ^2 indicates the changes in the model prediction when the variable indicated was removed from the model with both FPG and 2-h PG simultaneously. Subjects with previously diagnosed diabetes are excluded.

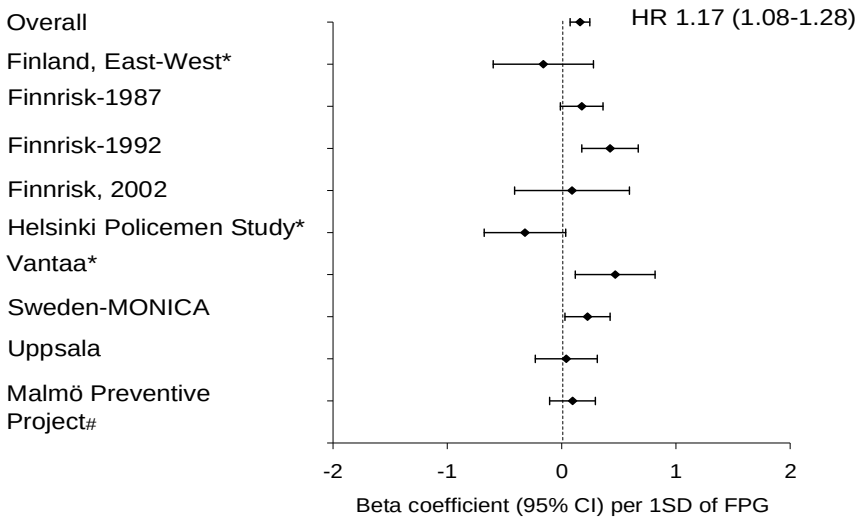
	Stroke incidence			
	Ischemic	**Hemorrhagic**	**Unspecified**	**All-causes**
Total	**n= 690**	**n= 180**	**n= 38**	**n= 908**
FPG	1.07 (0.98-1.17)	0.96 (0.78-1.17)	1.32 (1.04-1.68)	1.12 (1.04-1.21)
2h PG	1.12 (1.04-1.22)	0.97 (0.81-1.15)	1.36 (1.00-1.83)	1.14 (1.06-1.22)
χ^2 for FPG, 1 df (*p*)	0.02 *(0.88)*	0.08 *(0.78)*	1.27 *(0.26)*	0.79 *(0.37)*
χ^2 for 2-h PG, 1 df (*p*)	5.45 *(0.02)*	0.06 *(0.82)*	1.11 *(0.29)*	4.93 *(0.03)*

1 SD is 1.2 for FPG and 2.7 for 2-h PG.

Adjusted for age, study, BMI, total cholesterol, smoking, MAP and sex

a

Fasting plasma glucose



b

2-h plasma glucose

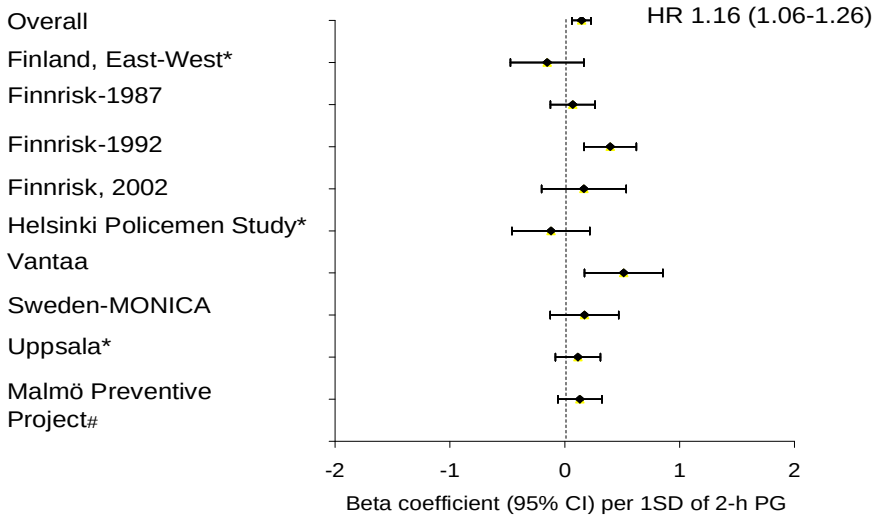


Figure 3. Individual and overall β- coefficients (♦) and 95 % confidence intervals (–) corresponding to a 1 SD increase in FPG (**Figure 3a**) and 2-h PG levels (**Figure 3b**) for ischemic stroke incidence. The analysis was adjusted for age, study, BMI, total cholesterol, MAP and smoking.
*Study includes only men, #Study includes only women

5.2. The impact of gender and age on CHD and stroke incidence (Article III-IV)

5.2.1. Charasteristics of participants

The baseline charasteristics of subjects according to age group and gender are shown in **Table 7**. Mean BMI and total cholesterol levels were higher in men than in women in the youngest age group (40-49 years), and similar in age group 50-59 years and tended to be lower in men than in women in age group 60-69 years. HDL was higher in women than in men in all age groups. Hypertension was more common in young men than in young women, but the difference leveled off in the oldest age group. The number of individuals with diabetes increased in both genders with increasing age and was higher in men compared with women. Smoking was less common in women than in men. The increase in trend between age groups for the prevalence of hypertension and diabetes was significant (p=0.001) in both genders. More women and men were smokers in the age group 40-49 years compared with the age groups 50-59 and 60-69 years.

In the non-diabetic population, the means of BMI and total cholesterol as well as the prevalence of hypertension were all higher in men than in women in the age group 40-49 years, but the gender differences leveled off with increasing age and became even or lower in men than in women in the age group 60-69 years. In non-diabetic women and men the increasing trend with aging was significant (p=0.001) for BMI, cholesterol and hypertension. Diabetic women were, however, more obese than diabetic men in all ages. HDL-cholesterol was higher in women than in men and smoking was more common in men than in women in all ages regardless of the diabetic status. The increasing trend in known CVD risk factors with aging in diabetic individuals was significant only for total cholesterol levels in women (**Table 8**).

Table 7. The baseline cahrasteristics of subjects according to age group and gender.

		Mean (SD)			No, (%)				
Age groups (yr)	***No, (%)***	***BMI (Kg/m^2)***	***Cholesterol (mmol/L)***	***HDL (mmol/L)***	***Hypertension***	***DM***	***Smoker***	***CHD***	**Ischemic stroke**
40-49									
Women	1380 (55.1)	26.1 (0.1)	5.70 (0.03)	1.56 (0.01)	575 (41.7)	64 (4.6)	336 (24.3)	24 (1.7)	14 (1.0)
Men	1125 (44.9)	26.9 (0.1)	6.18 (0.03)	1.28 (0.01)	600 (53.3)	65 (5.8)	350 (31.1)	54 (4.8)	19 (1.7)
p-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.199*	*<0.001*	*<0.001*	*0.141*
50-59									
Women	2227 (54.8)	27.6 (0.1)	6.22 (0.02)	1.61 (0.01)	1387 (62.3)	147 (6.6)	406 (18.2)	69 (3.1)	47 (2.1)
Men	1837 (45.2)	27.7 (0.1)	6.15 (0.03)	1.30 (0.01)	1247 (67.9)	195 (10.6)	550 (29.9)	155 (8.4)	57 (3.1)
p-value		*0.396*	*0.033*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.046*
60-69									
Women	1504 (55.5)	28.1 (0.1)	6.44 (0.03)	1.54 (0.01)	1138 (75.7)	173 (11.5)	200 (13.3)	89 (5.9)	68 (4.5)
Men	1205 (44.5)	27.4 (0.1)	6.01 (0.03)	1.28 (0.01)	920 (76.3)	182 (15.1)	280 (23.2)	139 (11.5)	61 (5.1)
p-value		*<0.001*	*<0.001*	*<0.001*	*0.679*	*0.006*	*<0.001*	*<0.001*	*0.511*
Total									
Women	5111 (55.1)	27.3 (0.1)	6.15 (0.02)	1.58 (0.01)	3100 (60.7)	384 (7.5)	942 (18.4)	182 (3.6)	129 (2.5)
Men	4167 (44.9)	27.4 (0.1)	6.12 (0.02)	1.29 (0.01)	2767 (66.4)	442 (10.6)	1180 (28.3)	348 (8.4)	137 (3.3)
p-value		*0.299*	*0.270*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*0.028*

Table 8. Baseline characteristics and the incidence of cardiovascular end points in women and men according to age groups and diabetic status.

	Age Groups, years								
	40-49			50-59			60-69		
Non-diabetic	**Women**	**Men**	***p-value***	**Women**	**Men**	***p-value***	**Women**	**Men**	***p-value***
No, (%)	1316 (95.4)	1060 (94.2)		2080 (93.4)	1642 (89.4)		1331 (88.5)	1023 (84.9)	
BMI (Kg/m^2)	25.87 (0.12)	26.75 (0.11)	*<0.001*	27.28 (0.10)	27.45 (0.09)	*0.226*	27.78 (0.13)	27.11 (0.11)	*<0.001*
Cholesterol (mmol/L)	5.69 (0.03)	6.18 (0.03)	*<0.001*	6.23 (0.03)	6.18 (0.03)	*0.072*	6.44 (0.03)	6.02 (0.03)	*<0.001*
HDL (mmol/L)	1.57 (0.01)	1.29 (0.01)	*<0.001*	1.62 (0.01)	1.31 (0.01)	*<0.001*	1.57 (0.01)	1.28 (0.01)	*<0.001*
Hypertension (Yes/No)	537 (40.8)	551 (52.0)	*<0.001*	1270 (61.1)	1085 (66.1)	*0.002*	988 (74.2)	766 (74.9)	*0.721*
Smoking vs. non-smoking	316 (24.0)	322 (30.4)	*<0.001*	374 (18.0)	488 (29.7)	*<0.001*	177 (13.3)	240 (23.5)	*<0.001*
CHD	20 (1.5)	47 (4.4)	*<0.001*	57 (2.7)	132 (8.0)	*<0.001*	68 (5.1)	114 (11.1)	*<0.001*
Ischemic stroke	12 (0.9)	16 (1.5)	*0.180*	43 (2.1)	48 (2.9)	*0.093*	52 (3.9)	44 (4.3)	*0.632*
Diabetic									
No, (%)	64 (4.6)	65 (5.8)		147 (6.6)	195 (10.6)		173 (11.5)	182 (15.1)	
BMI (Kg/m^2)	30.51 (0.83)	29.85 (0.65)	*0.584*	31.86 (0.48)	29.74 (0.31)	*<0.001*	30.41 (0.39)	29.25 (0.31)	*0.017*
Cholesterol (mmol/L)	5.88 (0.12)	6.24 (0.15)	*0.077*	6.11 (0.09)	5.94 (0.10)	*0.417*	6.43 (0.09)	5.95 (0.09)	*0.007*
HDL (mmol/L)	1.46 (0.06)	1.20 (0.05)	*<0.001*	1.41 (0.03)	1.24 (0.03)	*<0.001*	1.34 (0.03)	1.23 (0.02)	*<0.001*
Hypertension (Yes/No)	38 (59.4)	49 (75.4)	*0.052*	117 (79.6)	162 (83.1)	*0.410*	150 (86.7)	154 (84.6)	*0.575*

Smoking vs. non-smoking	20 (31.3)	28 (43.1)	0.117	32 (21.8)	62 (31.8)	<0.001	23 (13.3)	40 (22.0)	<0.001
CHD	4 (6.3)	7 (10.8)	*0.358*	12 (8.2)	23 (11.8)	*0.273*	21 (12.1)	25 (13.7)	*0.654*
Ischemic stroke	2 (3.1)	3 (4.6)	*0.661*	4 (2.7)	9 (4.6)	*0.364*	16 (9.2)	17 (9.3)	*0.976*

Data are given as means (standard error) adjusted for age, study and sex, or as number (%).
p-values reflect differences between men and women.

5.2.2. The incidence of coronary heart disease and ischemic stroke, and their risk factors in relation to age and gender

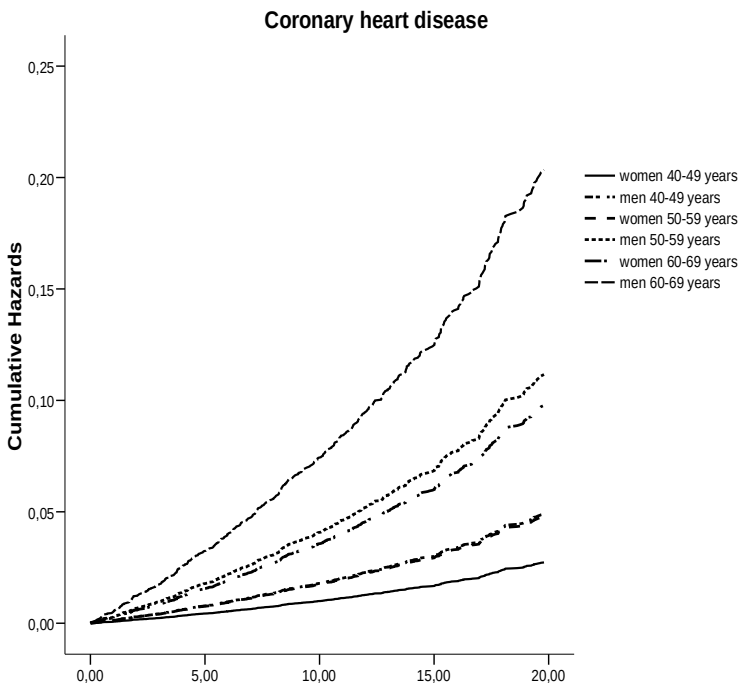
Men of all ages had higher incidence of acute CHD and ischemic stroke than did women, but the difference was more prominent for CHD than for ischemic stroke. Compared with the women aged 40-49 years the multivariate adjusted (age, study, hypertension status, BMI, total serum cholesterol, HDL-cholesterol and smoking status) hazards ratios of acute CHD and ischemic stroke increased in older age groups in both genders, and were higher for men than for women given the same age. The gender difference in the hazard ratios was, however, smaller for ischemic stroke than for CHD (**Table 9**).

The cumulative hazard ratios increased with increasing age in both genders. The risk for CHD incidence was highest in men age group 60-69 years and lowest in women in the age group 40-49 years. The risk was higher in men than in women in all age groups (**Figure 4a**). For ischemic stroke risk the gender differences smaller than that for CHD, being slightly higher in men than in women across age groups (**Figure 4b)**.

Table 9. Hazard ratios (HR) and incidence rates per 1000 person-years by 10- year age groups, for coronary heart disease, ischemic stroke. Women 40-49 years are used as the reference group.

Age groups (yr)	**40-49**		**50-59**		**60-69**	
	Women	**Men**	**Women**	**Men**	**Women**	**Men**
Coronary heart disease						
No (No/1000 Person-years)	24 (1.26)	54 (3.41)	69 (2.51)	155 (7.10)	89 (5.42)	139 (11.62)
HR (95% CI)	1	1.82 (1.12-2.97)	1.71 (1.07-2.74)	3.87 (2.49-6.02)	3.49 (2.18-5.57)	7.22 (4.59-11.36)
Ischemic stroke						
No (No/1000 Person-years)	14 (0.74)	19 (1.20)	47 (1.71)	57 (2.61)	68 (4.14)	61 (5.10)
HR (95% CI)	1	1.26 (0.62-2.55)	2.17 (1.18-3.97)	2.64 (1.45-4.82)	4.89 (2.67-8.97)	5.19 (2.81-9.58)

a



b

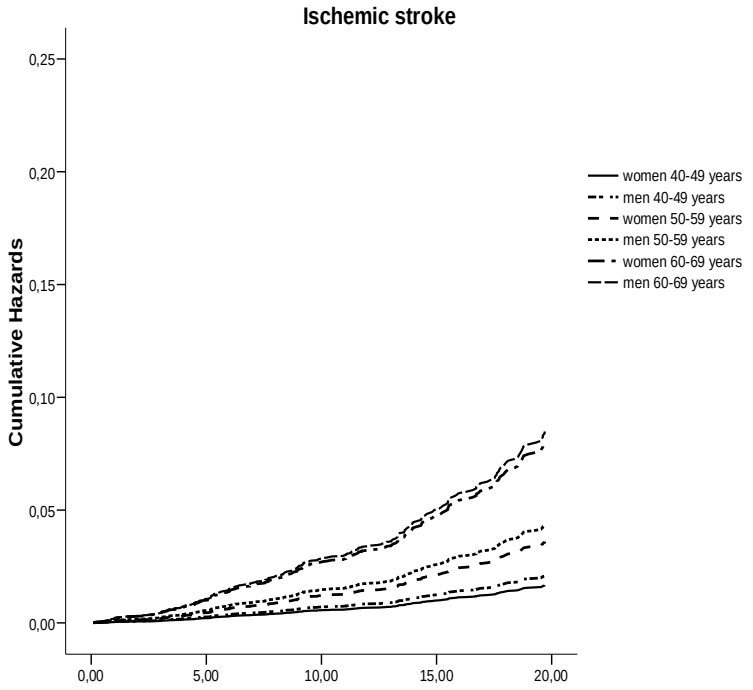


Figure 5. Cumulative hazards for coronary heart disease (**Figure 4a**) and ischemic stroke (**Figure 4b**) incidence in 10- year age groups in women and men. Women aged 40-49 years are used as the reference group. The analysis were adjusted for BMI, total cholesterol, HDL-cholesterol and status of diabetes mellitus, hypertension and smoking.

Ageing increased the risk for ischemic stroke more markedly in women compared with men (**Table 10**). In addition to ageing, smoking, diabetes and elevated cholesterol levels were all risk predictors for CHD incidence, but elevated blood pressure rather than cholesterol levels predicted the ischemic stroke incidence (**Table 10**).

Table 10. Hazard ratios for coronary heart disease and ischemic stroke, corresponding to a one SD increase in continuous variables or as indicated.

	Coronary heart disease		Ischemic stroke	
	Women	**Men**	**Women**	**Men**
Age (10 yrs)	2.07 (1.52-2.81)	2.35 (1.92-2.87)	3.36 (2.31-4.88)	2.38 (1.67-3.39)
BMI, kg/m^2	1.22 (1.05-1.42)	1.06 (0.93-1.19)	1.01 (0.83-1.22)	1.14 (0.94-1.39)
2-h PG mmol/l∗	1.14 (0.99-1.32)	1.12 (1.00-1.26)	1.03 (0.84-1.25)	1.23 (1.03-1.47)
FPG mmol/l∗	1.00 (0.80-1.25)	1.19 (1.06-1.34)	1.27 (1.04-1.56)	1.13 (0.90-1.44)
Cholesterol, mmol/l	1.20 (1.03-1.39)	1.37 (1.23-1.52)	0.90 (0.75-1.09)	0.96 (0.79-1.16)
HDL, mmol/l	0.77 (0.64-0.93)	0.84 (0.74-0.95)	0.81 (0.65-1.01)	0.97 (0.78-1.19)
Hypertension (Yes/No)	1.39 (0.94-2.06)	1.19 (0.91-1.56)	2.21 (1.33-3.68)	1.20 (0.75-1.91)
Smoking vs. non-smoking	3.10 (2.13-4.50)	1.99 (1.52-2.60)	1.38 (0.80-2.39)	1.89 (1.17-3.06)
Diabetes mellitus (Yes/No) ∗	2.44 (1.66-3.59)	2.10 (1.55-2.84)	2.24 (1.38-3.64)	2.97 (1.93-4.57)

∗Fitted in three separate model

5.2.3. The impact of diabetes on the incidence of coronary heart disease and ischemic stroke

The event rates for acute CHD and ischemic stroke were higher in men with and without diabetes compared with their female counterparts. The gender difference for CHD was larger in the non-diabetic than in the diabetic individuals, whereas this was not as substantial for ischemic stroke as for CHD. The multivariate-adjusted hazard ratios of acute CHD events increased with aging and diabetes, and were higher in men both with and without diabetes compared with age matched women, but the gender difference was diminished in diabetic individuals. In contrast, the gender difference with the ischemic stroke was enlarged in the diabetic population probably because the risk of ischemic stroke increased more in diabetic men than in diabetic women (**Table 11**). Diabetes and aging were associated with an increased risk of acute CHD and ischemic stroke events in both gender, however, diabetes was a stronger risk predictor for the risk of ischemic stroke than for CHD. Cholesterol predicted the risk of acute CHD, but not ischemic stroke event, in both genders. FPG and 2-h PG levels were CHD risk predictors only in men, whereas FPG predicted ischemic stroke risk in women and 2-h PG in men only. Hypertension increased the acute ischemic stroke risk, and BMI CHD risk only in women (**Table 12**).

Table 11. Event rates per 1000 person-years and hazard ratios (95% confidence intervals) for acute CHD and ischemic stroke events by diabetic status (partly unpublished data).

		Non-diabetic			Diabetic		
		Age groups, yr			Age groups, yr		
		40-49	50-59	60-69	40-49	50-59	60-69
CHD							
Rates							
Women		1.09 (0.68-1.65)	2.20 (1.68-2.83)	4.61 (3.61-5.81)	5.68 (1.80-13.69)	7.50 (4.06-12.74)	12.53 (7.96-18.82)
Men		3.11 (2.31-4.10)	6.57 (5.52-7.77)	10.82 (8.97-12.95)	9.62 (4.21-19.03)	13.24 (8.59-19.55)	17.51 (11.59-25.47)
HRs	**Adjustment**						
Model 1	Study						
Women		1	2.10 (1.26-3.49)	4.91 (2.97-8.12)	6.09 (2.08-17.82)	7.95 (3.88-16.26)	14.65 (7.87-27.28)
Men		2.90 (1.72-4.90)	6.43 (4.02-10.29)	12.34 (7.62-19.97)	10.44 (4.41-24.70)	15.98 (8.76-29.15)	22.54 (12.41-40.97)
Model 2	Model 1+ BMI						
Women		1	1.99 (1.20-3.32)	4.57 (2.76-7.58)	5.07 (1.72-14.92)	6.59 (3.20-13.61)	12.23 (6.52-22.96)
Men		2.81 (1.67-4.75)	6.13 (3.82-9.81)	11.91 (7.36-19.29)	8.94 (3.76-21.26)	14.26 (7.79-26.09)	19.78 (10.84-36.09)
Model 3	Model 2 +hypertension						
Women		1	1.91 (1.14-3.18)	4.26 (2.56-7.08)	5.05 (1.71-14.85)	6.19 (3.00-12.78)	11.28 (6.00-21.21)
Men		2.76 (1.63-4.66)	5.79 (3.61-9.29)	11.04 (6.80-17.93)	8.44 (3.55-20.09)	12.95 (7.05-23.77)	18.08 (9.88-33.10)

Model 4	Model 3+ total cholesterol, HDL-cholesterol						
Women		1	1.67 (1.00-2.79)	3.46 (2.07-5.77)	4.54 (1.54-13.36)	5.40 (2.62-11.14)	8.50 (4.50-16.03)
Men		2.07 (1.22-3.52)	4.35 (2.70-7.03)	8.38 (5.13-13.70)	6.10 (2.55-14.58)	10.14 (5.50-18.70)	14.24 (7.74-26.20)
Model 5	Model 4+ smoking						
Women		1	1.78 (1.06-2.97)	3.75 (2.24-6.26)	4.35 (1.48-12.80)	5.49 (2.66-11.33)	8.84 (4.68-16.72)
Men		1.94 (1.14-3.29)	4.23 (2.61-6.84)	8.40 (5.13-13.76)	5.40 (2.26-12.93)	9.54 (5.17-17.63)	13.76 (7.47-25.34)
Ischemic stroke Rates							
Women		0.65 (0.35-1.11)	1.66 (1.22-2.22)	3.53 (2.66-4.59)	2.84 (0.48-9.38)	2.50 (0.79-6.03)	9.54 (5.65-15.17)
Men		1.06 (0.63-1.68)	2.39 (1.78-3.14)	4.18 (3.07-5.56)	4.12 (1.05-11.22)	5.18 (2.53-9.50)	11.91 (7.17-18.68)
HRs	Adjustment						
Model 1	Study						
Women		1	2.62 (1.38-4.97)	5.71 (3.01-10.81)	5.08 (1.14-22.72)	4.23 (1.36-13.12)	17.78 (8.26-38.30)
Men		1.63 (0.77-3.43)	3.86 (2.05-7.26)	7.15 (3.73-13.69)	7.87 (2.22-27.93)	10.60 (4.46-25.20)	27.22 (12.76-58.10)
Model 2	Model 1+ BMI						
Women		1	2.54 (1.34-4.83)	5.46 (2.88-10.38)	4.57 (1.02-20.55)	3.78 (1.21-11.83)	16.14 (7.42-35.10)
Men		1.59 (0.75-3.37)	3.75 (1.99-7.06)	6.99 (3.65-13.39)	7.21 (2.02-25.72)	9.90 (4.15-23.66)	25.23 (11.75-54.19)
Model 3	Model 2 +hypertension						
Women		1	2.33 (1.23-4.44)	4.80 (2.52-9.14)	4.47 (0.99-20.13)	3.33 (1.06-10.44)	13.81 (6.33-30.15)

Men		1.53 (0.72-3.24)	3.37 (1.78-6.36)	6.07 (3.16-11.69)	6.47 (1.81-23.11)	8.28 (3.45-19.85)	21.42 (9.92-46.26)
Model 4	Model 3+ total cholesterol, HDL-cholesterol						
Women		1	2.39 (1.25-4.56)	4.92 (2.56-9.44)	4.21 (0.94-18.99)	3.28 (1.05-10.28)	13.36 (6.08-29.40)
Men		1.36 (0.64-2.91)	3.00 (1.57-5.72)	5.37 (2.76-10.44)	5.62 (1.56-20.21)	7.26 (3.01-17.52)	18.93 (8.70-41.19)
Model 5	Model 4+ smoking						
Women		1	2.48 (1.30-4.73)	5.17 (2.69-9.94)	4.14 (0.92-18.66)	3.32 (1.06-10.43)	13.91 (6.31-30.66)
Men		1.26 (0.59-2.70)	2.83 (1.48-5.42)	5.11 (2.62-9.97)	4.91 (1.36-17.74)	6.75 (2.79-16.32)	18.06 (8.29-39.37)

Table 12. Hazard ratios (95% confidence intervals) corresponding to a one SD increase in continuous variables or as indicated.

	CHD		Ischemic stroke	
	Women	**Men**	**Women**	**Men**
Age, 40-49 yrs	1	1	1	1
Age, 50-59 yrs	1.70 (1.06-2.75)	2.16 (1.58-2.95)	2.16 (1.17-3.98)	2.12 (1.26-3.58)
Age, 60-69 yrs	3.53 (2.15-5.79)	3.99 (2.85-5.58)	5.49 (2.93-10.28)	3.63 (2.06-6.38)
BMI, kg/m^2	1.22 (1.06-1.40)	1.02 (0.91-1.14)	0.97 (0.81-1.16)	1.05 (0.88-1.26)
Cholesterol, mmol/l	1.25 (1.09-1.43)	1.34 (1.22-1.49)	0.94 (0.79-1.12)	1.00 (0.85-1.19)
HDL, mmol/l	0.71 (0.59-0.85)	0.84 (0.74-0.94)	0.79 (0.64-0.97)	0.90 (0.75-1.09)
Hypertension (Yes/No)	1.51 (1.03-2.21)	1.27 (0.97-1.65)	2.33 (1.42-3.81)	1.47 (0.94-2.30)
Smoking vs. non-smoking	2.81 (1.97-4.01)	1.95 (1.51-2.52)	1.16 (0.67-1.99)	2.06 (1.33-3.19)
Diabetes mellitus (Yes/No)	2.48 (1.69-3.65)	2.09 (1.55-2.82)	2.37 (1.46-3.84)	3.01 (1.95-4.64)

6 DISCUSSION

6.1. Study design and methodology

The strength of the DECODE study was the long-length of follow-up and the collaborative data analysis, which gives more statistical power and possibility for a detailed analysis between gender and different age groups than if the analysis was performed individually by the individual study centres. The current study covers population cohorts from nine different European countries. However, different cultural background, which exists in between European populations, is associated with many factors such as different living conditions and life style factors that may results in differences in risk factor profiles and thus CVD outcome in between individual centres. Thus, more studies on the field are required.

Even though, the classification of CHD and stroke death from death certificates is not perfect, the principle of death certification has been the same for both gender and for all risk factor strata. The CHD and stroke mortality and incidence have also been uniformly classified with codes of International Classification of Diseases. Furthermore, in Finland and Sweden the national death and hospital discharge registers provide complete follow-up information for outcomes and the accuracy of the CHD and stroke diagnoses in the Hospital Discharge Register and Causes of Death Register when comparing the CHD and stroke events to the data provided by the population-based CHD and stroke registers in Finland and Sweden has been found to be fairly good. As the individual surveys have been conducted independently some variations exists in laboratory measurement methods in between the different cohorts. Thus, in order to make up the differences between studies, the analysis was adjusted for "cohort". Also, to take into account the differences in study protocols and the laboratory measures between studies, study-and- sex specific SD was used to standardize the variables in the collaborative data analysis.

Information on the other known CHD and stroke risk factors such as diet, alcohol use, psychosocial factors, physical activity and family history of CVD were not available and not taken into account in the present analysis.

The strength of the present study is that all the cohorts used in the study had data available for both FPG and 2-h glucose levels. This is the first study to investigate the question of glucose levels and the risk of stroke in a study group where all participants had had a 75g 2-h oral glucose tolerance test. The collaborative data analysis in the DECODE study provides an economic and efficient use of excisting population-based databases.

6.2. Interpretation of the findings

6.2.1. The impact of hyperglycemia on stroke mortality

The findings in rticle I showed that hyperglycemia and diabetes defined by either FPG or 2-h PG increases the risk of stroke mortality both in women and in men. These findings confirmed previous findings (Burchfiel et al., 1994; Hart et al., 1999; Kissela et al., 2005; Hu et al., 2005c; Hu et al., 2006; Mulnier et al., 2006) despite the differences in the methods used for the definition of hyperglycemia and diagnosis of diabetes. Several studies have reported hyperglycemia to increase the risk of CVD in non-diabetic individuals

(DECODE Study group, 2003a, Levitan et al., 2004; Lawlor et al., 2007). The oral glucose tolerance test has not been widely applied thus studies comparing the stroke risk between 2-hour post-load hyperglycemia and fasting hyperglycemia are scarce. We found FPG to better predict stroke mortality in women and 2-h PG in men in subjects without diabetes at baseline.

The underlying physiological base of IFG and IGT is different. Isolated IFG is mainly associated with hepatic insulin resistance and decreased first-phase insulin secretion, wheras isolated IGT is associated with peripheral insulin resistance and impairment of both early- and late-phase insulin responses (Abdul-Ghani, 2006). Men have been reported to have lower levels of beta cell function and higher prevalence of IFG compared with women, and women lower insulin sensitivity and higher prevalence of IGT compared with men (Williams et al., 2003). Thus, the gender differences in stroke mortality related to IFG and IGT categories found in the present study could partly be exlained by the metabolic differences and differences in prevalence of IFG and IGT in women and men.

6.2.2. The impact of hyperglycemia on the incidence of ischemic and hemorrhagic stroke

A significant association was found between diabetes, both previously diagnosed and screen-detected, and an increased risk of ischemic stroke in the present study (Article II). These results are consistent with other population based epidemiological studies (Janghorbani et al., 2007, Woodward et al., 2003). Increased risk of ischemic stroke has also been found in individuals with elevated serum fasting (Song et al., 2005) and nonfasting glucose levels (Lund-Håheim et al., 2006). This study showed that in individuals without previous diagnosis of diabetes the risk of ischemic stroke increased with increasing FPG and 2-h PG levels. The risk was more significant for elevated 2-h PG compared with FPG levels. Studies have found an increased risk (Zia et al., 2005) of hemorrhagic stroke in individuals with diabetes diagnosed by fasting glucose levels, no association in individuals with overt diabetes (Inagawa et al., 2007) or with diabetes defined by 1- h postload glucose measurement (Burchfiel et al., 1994) or a decreased risk (Jorgensen et al., 1994; Megherbi et al., 2003) in individuals with overt diabetes. In the present study we found no relationship between hyperglycemia and the risk of hemorrhagic stroke.

The etiology and pathophysiology of the ischemic and hemorrhagic stroke are different (Collins, 2007). Ischemic stroke is caused by impaired or cessation of blood flow to the brain, which may result in brain ischemia (Frosch et al., 2005), whereas hemorrhagic stroke results from a rupture in a cerebral blood vessel, which causes bleeding into the brain tissue (Collins, 2007). The main causes of acute ischemic stroke are large-artery atherosclerosis, caused by atherosclerosis in the internal carotid or vertebral-basilar arteries (Fisher et al., 2005), small-vessel disease with formation of microatheroma in deep, small penetrating arteries and cardioembolism are the main causes of acute ischemic stroke (Fisher et al., 2008). Hypertension is a common cause for hemorrhagic stroke (Qureshi et al., 1997; Woo et al., 2002; Ariesen et al., 2003). The different pathophysiology and etiology behind ischemic and hemorrhagic stroke could also indicate different risk factors for the two stroke sub-types and could explain the differences found in the present study between ischemic and hemorrhagic stroke. Further studies are needed to clarify the issue.

6.2.3. Age and gender difference in the incidence of coronary heart disease or stroke

In the present study (Article III) we found mean BMI and total cholesterol levels to be higher in men than in women in younger ages (40-49 years at baseline), and similar in the middle age group (50-59 years) and somewhat lower in men than in women in the oldest age group (60-69 years). In women HDL was higher compared with men in all age groups. Hypertension was more common in young men than in young women, but the difference leveled off in the oldest age group. The number of individuals with diabetes was higher in men than in women across age groups, but increased with age in both genders. Smoking was more common in men than in women.

Men had a higher incidence of acute CHD and ischemic stroke compared with women at all ages. The difference between genders was more prominent for CHD than for ischemic stroke incidence. Compared with women aged 40-49 years the multivariate adjusted hazards ratios of acute CHD and ischemic stroke increased in older age groups in both genders, and were higher for men than for women given the same age. The gender difference in the hazard ratios was, however, smaller for ischemic stroke than for CHD. We found that aging was clearly associated with an increase in ischemic stroke, and this trend was more prominent in women than in men. The incidence of CHD and ischemic stroke were significantly higher (4.3 and 5.6 times, respectively) in women in the oldest age group compared with the youngest age group; this age-related increasing trend in incidence of CHD and ischemic stroke was, however, less marked in men (3.4 and 4.3, respectively) than in women. We found a 10- year lag in the development of CHD and stroke in women compared with men. Our findings are consistent with previous reports regarding gender difference in CHD and stroke incidence (Lerner et al., 1986; Isles et al., 1992; Jousilahti et al., 1999; Rosamond et al., 2007). Both in women and in men age, smoking, diabetes and elevated cholesterol levels were risk predictors for CHD incidence. Additionally, 2-h PG was a CHD risk predictor in men and BMI in women. The risk predictors for the ischemic stroke incidence were otherwise similar, but elevated blood pressure instead of serum cholesterol levels was a significant risk predictor in both genders.

Recent population based studies have found clear differences between risk factors for the diseases of the circulatory system CHD, stroke and peripheral artery disease (Glynn et al., 2005; Wilhelmsen et al., 2005). Research has also indicated that different vascular sites may respond differently to different set of risk factors (DeBakey et al., 2000; Paraskevas et al., 2008). The Rotterdam Study found a more pronounced gender difference in the degree of atherosclerosis in coronary vessels compared with other vascular beds (Kardys et al., 2007). Thus, as also found in the present study, different risk factors could contribute differently in the development of CHD and stroke and these risk factors may differ by gender. The fact that fewer women smoked than men and the earlier exposure to the CVD risk factors in men and the more favorable HDL profile in women may also partly explain the gender difference found in the present study. Other factors such as the menopause status (Andreotti, 2008) and transition (Janssen et al., 2008), the management of risk factors (Andreotti, 2008; Jairath, 2001; Stramba-Badiale, 2006) may also have contributed to the observed gender difference in CHD and ischemic stroke incidence, and need to be studied in more details.

6.2.4. Age and gender difference in the incidence of coronary heart disease and ischemic stroke in diabetic and non-diabetic individuals

The results in Article IV showed that both non-diabetic and diabetic men have a higher risk of CHD than their female counterparts, but the gender difference is not as pronounced in the

diabetic as in the non-diabetic populations. In contrast, diabetic men have higher rates of ischemic stroke events than diabetic women but the event rates do not differ much in the non-diabetic population. Several studies have found diabetes to increase the risk of CHD (Jousilahti et al., 1999; Laakso et al., 2001; Howard et al., 2006) and stroke (Tuomilehto et al., 1996; Hart et al. 2000; Almdal et al., 2004) in both genders. Diabetes has been reported to increase the risk of CHD (Lee et al., 2000; Kanaya et al., 2002; Huxley et al., 2006) and stroke (Lehto et al., 1996; Hart et al., 2000; Almdal et al., 2004) more markedly in women than in men. These studies have, however, used non-diabetic women and non-diabetic men as reference groups for women and for men, respectively, when they calculated the relative risk for diabetic individuals. In the present study in order to make the relative risk directly comparable between women and men, non-diabetic women in the youngest age group was used as a reference group for both women and men of all other age groups. Contradictory to the previous reports on stroke we found in the present study a more markedly increased risk of acute ischemic stroke events in diabetic men compared with diabetic women. But in the present study we could not examine whether this is true for hemorrhagic stroke or for the subtypes of ischemic stroke due to the low number of the hemorrhagic stroke events and inability of further classification of individuals into subtypes of the ischemic stroke. Previous studies with both ischemic and hemorrhagic stroke have shown a higher relative stroke risk in diabetic women than in diabetic men (Lehto et al., 1996; Hart et al., 2000; Almdal et al., 2004), Studies have also reported the risk of certain subtypes of ischemic or hemorrhagic stroke to differ between women and men (Roquer et al., 2003; Thrift et al., 2009). This might have affected the observations in the current study and needs to be explored in more detail in the future.

In the present study we found non-diabetic men to have higher rates of smoking, hypertension and abnormalities of lipid profiles compared with non-diabetic women. This could partly explain the higher CHD risk in non-diabetic men compared with non-diabetic women. Also, other factors such as the menopause status (Andreotti et al., 2008) and the management of risk factors (Andreotti et al., 2008; Jairath et al., 2001) may have contributed to the observed gender difference in CHD and ischemic stroke incidence found in the present study. We found obesity and cholesterol levels to be higher in diabetic women compared with diabetic men, which may partly explain the smaller gender difference in CHD risk in diabetic population. Even though, CHD and stroke have some common aspects, the reactivity of coronary and cerebral arteries to the CVD risk factors, environmental and genetic factors, has been found to differ (Puddu et al., 1995). Thus, as found in the present study the known CVD risk factors including diabetes may contribute differently to the development of CHD and the ischemic stroke, and partly explain the gender difference in the risk of CHD and ischemic stroke incidence found in diabetic individuals in the present study.

7 CONCLUSIONS

The conclusions related to the study objectives are:

1. In individuals without diabetes at baseline, the FPG criteria for diabetes compared with the 2-h PG criteria better predicted stroke mortality in women, whereas the latter was better than the former in men. The underlying pathophysiology of IFG and IGT is different and the prevalence of IFG and IGT differs between genders. Thus, also the stroke mortality in relation to the two glucose categories may differ in between women and men.

2. In individuals without a prior history of diabetes, elevated 2-h PG, but not FPG levels, predicted ischemic stroke incidence. Neither FPG nor 2-h PG predicted the incidence of hemorrhagic stroke. The different pathophysiology and etiology behind ischemic and hemorrhagic stroke could indicate different risk factors for the two stroke sub-types. Further studies are needed to clarify the issue.

3. The relative risk of acute CHD and ischemic stroke was higher in men than in women in all ages, but the gender difference was more marked for CHD than for ischemic stroke. Aging and diabetes contributed to the development of CHD and ischemic stroke in both genders. BMI was a risk predictor for CHD incidence and hypertension and FPG for ischemic stroke incidence only in women. The 2-h PG predicted CHD and smoking predicted ischemic stroke incidence only in men.

4. CHD risk was higher in men than in women but difference was not as pronounced in diabetic population. Diabetes, increased ischemic stroke risk more in men than in women. The proper understanding of reasons for the gender difference in CHD and ischemic stroke is important in developing effective interventions and treatment strategies for the two diseases.

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Appendix 1. Information on blood glucose sampling and testing

Population and code	Blood sample	Glucose load (g)	Fasting time (hour)	Time of day of blood sampling (hour)	Method of glucose assay
Finland, East-West†	Venous Plasma	75	overnight	8:00-10:00 am	glucose dehydrogenase, (Beckmann, Brea, Ca. USA)
National FINRISK Study	Plasma	75	>8	8.00-11.00 am	Hexokinase assay (Thermo Electron Oy)
Helsinki Policemen Study†	Venous whole blood	75			
Vantaa	Venous whole blood?	75	overnight		Glucose oxidase (Beckman Instruments, Fullerton, California)
Italy, Cremona	Venous plasma	75, monohydrate	≥12	8:30-10:30 am	GOD-PAP glucose-oxidase (Boehringer Mannheim, Milan, Italy)
Malmö Preventive Project	Plasma	75	overnight		
The Netherlands, Hoorn Study	Venous Plasma	75, anhydrate	≥10	8:00-10:00 am	glucose dehydrogenase (Merck, Darmstadt, Germany)
Zuthpen Study†	Venous Plasma	75	overnight	8:00-10:00 am	hexokinase (Abbott Epx)
Sweden, MONICA	Plasma	75	>10	7:45-10:00	glucose oxidase (Beckman analyzer)
Uppsala†	Venous Plasma	75			glucose dehydrogenase-photspectrometric (Gluc-DH, Merck, Darmstadt, Germany)
U.K., Goodinge	Plasma	75	overnight	morning	glucose-oxidase (Beckman, Brea, California)
Newcastle	Venous Plasma	75	overnight	8:00-10:00 am	hexokinase (Abbott Epx)

Appendix 2. Information on lipid assays

Population and code	Blood sample	Triglycerides	HDL	Cholesterol	LDL	Methodology
Finland, East-West†	venous Plasma	+	+	+	+	
National FINRISK Study	Serum	+	+	+	-	Enzymatic techniques (CHOD/PAP) Optima, Thermo Electron Oy
Helsinki Policemen Study†	venous whole blood	+	-	+	-	
Vantaa	Serum	+	+	+	-	Enzymatic techniques (Boehringer-Mannheim)
Italy, Cremona	venous Plasma	+	+	+	-	Enzymatic techniques (Boehringer-Mannheim)
Malmö Preventive Project	plasma	+	-	+	-	
The Netherlands, Hoorn Study	Serum	+	+	+	+	Enzymatic techniques (Boehringer-Mannheim)
Zuthpen Study†	venous Plasma	+	+	+	-	
Sweden, MONICA	Serum	+	+	+	-	Enzymatic techniques (Boehringer-Mannheim)
Uppsala†	Serum	+	+	+	-	Enzymatic techniques (Instrumentation Laboratories, Lexington, USA) HDL particles were separated by precipitation with magnesium chloride/phosphotumgstate.
U.K., Goodinge	plasma	+	+	+	+	
Newcastle	venous Plasma	+	+	+	+	Cobas Bio centrifugal analyser, Toch Products Ltd, UK

*venous whole blood for fasting sample in 55-year-old population

Appendix 3. Information on physical examination

Population and code	Blood pressure	Waist	Hip
Finland, East-West[†] National FINRISK Study	Mercury sphygmomanometer, Reister, cuff size 14*40 cm. Measured three times in sitting position from right arm of the subject.	Midway between the lower rib margin and iliac crest	Widest circumference over the greater trochanters
Helsinki Policemen Study[†] Vantaa			
Italy, Cremona	Sphygmomanometer (BP-103N, Japan), it was taken twice (beginning and end of visit), in the sitting position, after 10 minutes rest and the lowest figure was considered	Measured at the level of umbilicus	Not measured; we measured thigh circumference at the level of the gluteal fold on the right thigh
Malmö Preventive Project	Sphygmomanometer, modifiable cuff width. Measured twice in the supine position after 10 min rest. Mean figure was recorded		
The Netherlands, Hoorn Study Zuthpen Study[†]	On the right arm with sphygmomanometer (Hawksley_Gelman Ltd)	Midway between the lower rib margin and iliac crest	Widest level over the greater trochanters
Sweden, MONICA	Random zero method	Midway between the lower rib margin and iliac crest	Maximum circumference over the buttocks
Uppsala[†]		Midway between the lowest rib and the iliac crest	Circumference over the widest part
U.K., Goodinge			
Newcastle	Measurements made following the protocol of the British Hypertension at the time of the study, so mercury sphyg with adult size cuff (12.5X32cm) for all. Right arm, sitting, mean of two measurements.	Midpoint between the lower costal margin and the superior iliac crest	Circumference over the greater trochanters

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